French-Speaking Society of Oral Medicine and Oral Surgery

USE OF VASOCONSTRICTORS IN ODONTOSTOMATOLOGY (*)

Recommendations

ORAL SURGERY-
ORAL MEDICINE

Working group:
Carlos Madrid (dentist, Toulouse, France), reporter
Bruno Courtois (dentist, Toulouse, France)
Marc Vironneau (anesthetist, Toulouse, France)

Reading group:
Jacques Bayssière (dentist, Montpellier, France) Jean-Pierre Bernard (stomatologist, Geneva, Switzerland) Jean-Loup Coudert (dentist, Lyons, France)
Damien Duran (dentist, Toulouse, France)
Ahmed Feki (dentist, Strasbourg, France)
Jean-Christophe Fricain (dentist, Bordeaux, France) Patrick Girard (dentist, Paris, France)
Jean-Claude Harnet (dentist, Strasbourg, France) Jacques Jeandot (dentist, Bordeaux, France)
Benoît Lefèvre (dentist, Reims, France) Dan Longrois (anesthetist, Nancy, France)
Louis Maman (dentist, Paris, France)
Gilbert de Mello (dentist, Rennes, France)
Guillaume Penel (dentist, Lille, France)
François Prédine-Hug (dentist, Brest, France)
Yvon Roche (dentist, Paris, France)
Jacky Samson (dentist, Geneva, Switzerland)
Jacques-Henri Torres (stomatologist, Montpellier, France) Daniel Viennet (dentist, Nancy, France)

GENERAL METHODOLOGY

These recommendations on the use of vasoconstrictors in odontostomatology were performed by a working group at the end of an analysis of the scientific literature and collection of the opinion of the members of the French-Speaking Society of Oral Medicine and Oral Surgery at a scientific meeting in Metz on 23 May 2002. The text was then submitted to a reading group before being definitively adopted.

The members of the reading and working groups were appointed by the French-Speaking Society of Oral Medicine and Oral Surgery. The working group was moderated by a spokesperson who compiled the final document before proposing and discussing it with the working group, then submitting it to the reading committee. A systematic bibliographic research was performed by interrogation of the Medline data base.

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This bibliography obtained in an automated way was supplemented by manual research. The members of the working group and reading group sent articles. The lists of references quoted in the articles already identified were consulted

The spokesperson used the reading grids designed to assess the methodological quality and the level of scientific proof of these documents, together with the working group. The documents were collated in various categories according to these grids. On the basis of this analysis of the literature, the working group proposed recommendations as many times as possible. These were based either on a level of scientific proof, or, in the absence of proof, on a professional agreement strongly produced during the scientific meeting of the French-Speaking Society of Oral Medicine and Oral Surgery on 23 May 2002.
The bibliography obtained was almost completely used so that the working group did not deem it useful to separate a selective bibliography and a complementary bibliography. On the other hand the complete bibliography obtained was collated analytically according to the level of proof (LoP) on the basis of the following classification (US Agency for Health Care Policy and Research):

Level I a: Proof of Randomized Controlled Trials (RCT) meta-analysis

Level I b: Proof based on at least one RCT

Level II a: Proof based on a non-randomized controlled study

Level II b: Proof based on a another non-randomized controlled study

Level III: Proof from a well defined descriptive experimental study (this includes comparative studies, cohort studies, and case control studies)

Level IV; Experts' opinion or clinical experience

Grades A, B and C are allocated to the recommendations according to the level of proof of the respective bibliography:

Grade A: Based on a level of proof I Grade B: Based on a level of proof I or III Grade C: Based on a level of proof IV

STRATEGY OF THE DOCUMENTARY RESEARCH

The automated research was based on the following key words:
- **local anaesthesia**
- **general anaesthesia**
- **vasoconstrictors**
- **nor-epinephrine**
- **epinephrine**
- **levonordefrin**
- **corbadrine**

The preceding key words were crossed with:
- **dentistry**
- **maxillofacial surgery**
- **side effects**
- **adverse effects**
- **special patients**

SELECTED QUESTIONS

- What is the place of vasoconstrictors in odontostomatology?
- Are vasoconstrictors necessary in odontostomatologic anesthesia?
- Can vasoconstrictors be useful in odontostomatologic practice apart from their association with the local anesthetic substance?
- Can vasoconstrictors be associated with general anesthetics (GA) during a general anesthesia in odontostomatology?
- How to choose the vasoconstrictor molecule in odontostomatology?
- What are the benefits and drawbacks of adrenaline and noradrenaline?
- What is the interest of other substances?
- What are the indications of vasoconstrictors in odontostomatology?
- What dosage must be applied to vasoconstrictors in odontostomatologic anesthesia?
- What are the drug interactions of vasoconstrictors used in odontostomatologic anesthesia?
- What are the affections that contra-indicate vasoconstrictors in odontostomatology?
- Do physiological conditions contra-indicate vasoconstrictors in odontostomatologic anesthesia?

RECOMMANDATIONS

Injection technique

1. The injection of an anesthetic solution with or without vasoconstrictor must always be performed slowly (1 ml per minute) and in a fractioned manner in order to monitor the potential signs of a harmful effect of the injection. When the injection takes place in a well vascularised territory, a negative aspiration test is a constant precondition for the injection of the anesthetic solution with or without vasoconstrictor. The smallest effective dose is always recommended. **[Grade C]**

Indications

2. Associating a vasoconstrictor and an anesthetic solution in local odontostomatologic anesthesia by infiltration is indicated since the vasoconstrictor decreases the intravascular injected mixture passage and thus ensures an increase in the duration and depth of the anesthesia while reducing the systemic effects of the solution. **[Grade A]**

3. It does not seem possible to formally conclude with respect to the safety of the retraction cords soaked with vasoconstrictor used in dental prosthesis. Evaluations on animals seem to show that the hemodynamic variations are inconstant. The literature reports a serious accident in man. **[Grade B]**

4. Local haemostatic techniques using pure vasoconstrictors or mixed with anesthetic or astringent substances have not been the subject of a published evaluation with a satisfactory proof level. Thus, they are empirical. Although largely distributed, they did not give rise to the accident or incident publication in connection with the vasoconstrictors. **[Grade C]**

5. The use of an anesthetic solution with a vasoconstrictor added as an agent to decrease the bleeding and to reduce the analgesia threshold among oral surgery patients under general anesthesia, is instrumental in decreasing the sympathetic response to the surgical aggression and to decreasing the necessary depth of the general anesthesia. **[Grade B]**

Choosing the method

6. From an industrial and medical point of view, adrenaline is the leader in vasoconstrictors used alone or in association with a local anesthetic in odontostomatology. It uses the broadest case-mix which confirms a high safety for this molecule. The non-catechol derivatives have not proven to date their superiority even among patients likely to not tolerate catecholamines well. **[Grade B]**

Indications according to the anesthesia technique

7. The use of a vasoconstrictor in casual anesthesia techniques (intrapulpal, intraligamentary and intraseptal anesthesia) is not essential but considerably improves the success rate, duration and depth of the anesthesia obtained. If the injection is performed under the proper conditions, the local lesions directly attributable to the vasoconstrictor are negligible and reversible. There are systemic effects of these injections but they are most often much lower than those observed in infiltration anesthesias. **[Grade A]**

8. The use of a vasoconstrictor in local anesthesia techniques (infiltration, lingual nerve anesthesia, buccal nerve anesthesia) is not essential but appreciably improves the success rate, duration and depth of the anesthesia obtained. **[Grade C]**

9. The addition of a vasoconstrictor to the anesthetic solution is not essential for the anesthesia of the mandibular foramen of the inferior alveolar nerve. The addition of adrenaline increases the duration of the anesthesia but does not seem to have a decisive effect on the incidence of failures. The results concerning the success rate of the anesthesia are contradictory. Taking into account the relation that exists between the success rate and the volume of the solution injected, the addition of a vasoconstrictor could be considered in the prevention of systemic effects of local anesthetics. **[Grade C]**

Dose of the vasoconstrictor

10. The results are contradictory on the subject of the ideal dosage of the adrenaline in lidocaine 2 % solutions. The solution at 1/200,000 gives a duration of effect sufficient for the majority of the odontostomatologic procedures. **For articaine 4% and mepivacaine 2%, solutions at 1/200,000 should be preferred in the absence of significant difference in performance with the solution at 1/100,000 and because they would probably be better tolerated. [Grade A]**

Drug interactions

11. The attitude towards patients under tricyclic antidepressants must be to disregard the noradrenaline in association with local anesthetics and to inject reduced amounts of local anesthetics associated with adrenaline at 1/200,000. In practice the amount injected should be one-third of the total amount for the normal subject. **[Grade C]**

12. Patients under cardio-selective beta-blockers can receive local anesthesias with vasoconstrictor (adrenaline at 1/200,000).

Among patients receiving non-selective beta-blockers it is recommended to use anesthetic solutions that are the most weakly dosed in vasoconstrictor. **[Grade C]**

13. Volatile halogen general anesthetics should not be used with adrenaline. The literature encourages prudence with regard to the use of local adrenaline anesthetics in case of association of thiopental + halothane during a general anesthesia. **[Grade C]**

14. Vasoconstrictors will be barred at least 24 hours after the consumption of cocaine to allow the elimination of the drug and its active metabolites. **[Grade C]**

15. No accident was reported with respect to the administration of local adrenaline anesthetic among patients under antipsychotics or alpha-blockers. The risk of interaction between these substances is theoretical in usual amounts in odontostomatologic anesthesia. **[Grade C]**

16. There is no contra-indication in the administration of local adrenaline anesthetic for patients under selective MAOI's. [Grade C]

Pathologies contra-indicating vasoconstrictors associated with the local anesthetic

17. The pheochromocytoma constitutes an absolute contra-indication of the vasoconstrictors. The patients affected with this affection must be treated in a hospital environment having a rehabilitation structure when a local anesthesia with or without vasoconstrictor is necessary. **[Grade C]**

18. It seems desirable to avoid the association of vasoconstrictors with the local anesthetic during conservative care and especially not conservative care on a bone irradiated beyond 40 Gy. **[Grade A]**

19. Intraosseous injections of local adrenaline anesthetic must be avoided among arrhythmic patients. **[Grade A]**

Pathologies not contra-indicating vasoconstrictors associated with the local anesthetic

20. Stabilized hyper and hypothyroid patients do not have major disorders when they are subjected to a corrective treatment and put in contact with catecholamines. Although the theoretic risk of thyroxine-adrenaline potentiation is serious, there are no reported clinical cases. **[Grade C]**

21. Vasoconstrictors associated with an anesthetic solution are not contra-indicated for a hypertensive subject stabilized by antihypertensive treatment. **[Grade A]**

22. In case of pressure instability associated with other elements encumbering the prognosis, care involving a local anesthesia with vasoconstrictor must be conducted in a hospital environment having a rehabilitation structure and performed under monitoring. **[Grade A].**

23. In the auricular fibrillations balanced by an adapted treatment the control of the stress and therapeutic heart rate is essential and the use of local anesthetics with vasoconstrictor is indicated. **[Grade C]**

23 Patients under digoxine and those affected with atrio-ventricular arrhythmias must be treated under monitoring in a hospital environment having a rehabilitation structure when a local anesthesia with or without vasoconstrictor is necessary. **[Grade C]**

24. **Vasoconstrictors associated with an anesthetic solution are not contra-indicated for stabilized coronary cardiopathies. [Grade C]**

25. Vasoconstrictors associated with an anesthetic solution are not contra-indicated for asthmatic subjects designed to monitor the pain and to avoid the stress which is probably the main trigger source for an asthma attack in the dental office. In case of corticodependent asthma, the recourse to an anesthetic without vasoconstrictor and thus without bisulphite is indicated. **[Grade C]**

26. Vasoconstrictors associated with an anesthetic solution are not contra-indicated among patients having presented old and cured viral or toxic liver damage. In case of severe evolutive attack, the assessment of the liver damage is important. The total quantity injected may have to be reduced and the intervals between the injections increased, without prejudice to the use of an associated vasoconstrictor. **[Grade C]**

27. Vasoconstrictors associated with an anesthetic solution are not contra-indicated for balanced type I or II diabetic patients. In case of unbalanced and unstable diabetes, abruptly going from hypo to hyperglycaemia, the quantities of local anesthetic with vasoconstrictor will be moderate so as to take into account the hyperglycaemic character of the adrenaline. **[Grade C]**

Physiological conditions and vasoconstrictors

29. Vasoconstrictors associated with an anesthetic solution are not contra-indicated during pregnancy and breastfeeding. The usual amounts may be used. **[Grade C]**

30. Vasoconstrictors associated with an anesthetic solution are not contra-indicated for children beyond six months. The total amount of local anesthetic with or without vasoconstrictor for the healthy adult must be divided by 3 below 15 kg and by 2 between 15 and 40 kg weight. **[Grade C]**

31. Vasoconstrictors associated with an anesthetic solution are not contra-indicated for elderly persons. The total amount of anesthetic with or without vasoconstrictor must be adapted to the metabolic condition of the subject considered. **[Grade C]**

RATIONALE

1. VASOCONSTRICTORS' PLACE IN ODONTOSTOMATOLOGY

Adrenergic vasoconstrictors are among the therapeutic substances administered most in odontostomatology. Their use in association with an anesthetic substance began in 1904 year when Heinreich Braun (1903), a renowned German specialist in local anesthesia, developed an adrenaline-procaine mixture marketed soon thereafter by Hoechst under the Novocaine® brand which would dominate the market for 50 years (Yagiela, 1995 [LoP IV]).

Vasoconstrictors are also responsible for more drug interactions than most other drug substances specific to the odontostomatologist (Yagiela, 1999 [LoP IV]). Adrenaline and other sympathomimetic amides derivatives are injected in a routine manner in association with local anesthetics (LA) to control the pain, or even alone on gingival retraction cords and in injectable or topical solutions designed to control local bleedings.

1.1. Are vasoconstrictors necessary in stomatological anesthesia?

The advantages of vasoconstrictors in odontostomatologic anesthesia are universally recognized by the scientific community and the main odontostomatologic local anesthesia manuals [LoP IV] refer to them as scientific evidence (Davies and Lefkowitz, 1981; Malamed, 1997; Berini and Gay, 1997; Gaudy and Arreto, 1999).

It is generally admitted that, whatever the mode of injection, the bioavailability of amino-amide type LAs is total. After injection a part of the dose joins its target while another fraction passes in systemic circulation. The passage through the endothelial vascular barrier is easy taking into account the good liposolubility of LA. A significant capillary density, a local blood flow and a high blood/tissue distribution coefficient are among the many growth factors in the systemic reabsorption which are joined together in most of the target territories of local anesthesia in the oral cavity. Various pharmacological interventions and in particular the addition of vasoconstrictors to the solution LA can appreciably modify the systemic reabsorption although it also varies with the proper effect of the LA used on local vascularisation (Viel et al. 1997 [LoP IV]

Thus, the vasoconstrictor initially acts like a substance likely to reduce the absorption speed of the anesthetic solution at the injection point (Fink et al., 1978 [LoP IIb] ; Jage, 1993 [LoP IV]). The reduction in the systemic reabsorption is associated with the local action of vasoconstrictors (adrenaline being selected as a reference) by stimulation of the alpha 1 receivers of the nonstriated muscles of the peripheral vessels. The consequence of this action is the decrease in the tissue perfusion which results in local ischaemia of the tissues (Allwood et al., 1963 [Not classified]).

This ischaemia also relates to the vasa nervorum which feed the axons of the sensitive nervous fibres concerned by the local anesthesia; a significant deceleration of the nervous cells metabolism follows and thus the nerve impulse transmission which leads to a deepening of the anesthesia and an increase in its duration.

The effect of the vasoconstrictor also comprises a facilitating action on the penetration of the LA, in the nervous fibre by direct stimulation of anti-nociceptive adrenergic receivers. Such an action has been demonstrated during eperidural and intrathecal injections (Bromage et al., 1983 [LoP IIb] ; Yaksh and Reddy, 1981 [LoP Ib]).

From a clinical point of view, the deceleration of the absorption speed leads to two demonstrated long-standing positive results:
(1) the increase in the duration of the anesthesia (Jage, 1993 [LoP IV]);
(2) the reduction of the plasmatic peak of the LA, which itself has two beneficial effects: the decrease in the systemic toxicity and as a corollary the possibility to increase the injected dose. Covino and Vassallo (1976) [LoP V] thus reported that the addition of adrenaline made it possible to increase by 200% the duration of lidocaine 0.5% anesthesia while decreasing the plasmatic peak by 50%. The behaviour of the other LA's tested is close.

Let us note, however, that one of the unexpected side effects of vasoconstrictors when they are associated with LA's is to slow down the administration of the anesthesia. Falaiye and Rood (1990) [LoP IIa] thus showed that the addition of adrenaline in a lidocaine solution appreciably delayed the administration of a major anesthesia assessed by pulp tester.

This side effect would be dependent at the same time on a barrier effect of the vasoconstrictor with regard to the anesthetic solution which it blocks on the injection site, at a distance from the specified nervous fibre, and an acidifying effect of the vasoconstrictor with respect to the environment which is favourable for maintaining the anesthetic in its inactive non-ionized form.

Associating a vasoconstrictor and an anesthetic solution in odontostomatology is thus indicated because the vasoconstrictor decreases the plasmatic reabsorption of the mixture injected and thus ensures an increase in the duration and depth of the anesthesia while reducing the systemic effects of the solution.

1.2. Can vasoconstrictors be useful in stomatological practice apart from their association with the local anesthetic substance?

Two fields of the odontostomatology use vasoconstrictors apart from anesthesia:

- on the one hand prosthesis: retraction cords designed to pursh the gum back below the enamel preparations and/or the dentine during the impression (Pallasch, 1998 [LoP IV]);
- on the other hand: oral and in particular endodontic surgery where among other solutions the injection of vasoconstrictors or the installation of supports containing vasoconstrictors were recommended to limit the bleeding in the surgical zone centre (Syngcuk and Sivakami, 1997 [LoP IV]).

1,2.1. Vasoconstrictors on the gingival retraction cords

Studies concerning the toxicity of gingival retraction cords charged with vasoactive substance (in practice 8% racemic adrenaline) are contradictory by the variance of the toxicological and pharmacokinetic results.

For 3 cm of cord Malamed (1997) [LoP IV] reports values going from 225.5 to 661 µg of racemic adrenaline which in reality represents 113 to 330 µg of the pharmacologically active L shape. Such a quantity is equivalent according to Pallasch (1998) [LoP IV] to 3.13 to 9.16 cartridges of 2 ml of anesthetic solution dosed at 1/100,000 of adrenaline.

Studies on tolerance showed dramatic elevations in the heart rate and blood pressure after inserting cords, for a dog. The plasmatic rate of adrenaline was measured for only one patient going from 15 pg.ml^{-1} to 316 pg. ml^{-1} after inserting cords without any hemodynamic effect. Houston et al. (1970) [LoP IIb] were interested in the possible hemodynamic effects of these cords. They use a poorly defined protocol on 9 subjects. Their results relate to the blood pressure and heart rate at various times of an impression. They show negligible hemodynamic variations.

Other research highlights a significant difference in the systemic reabsorption according to whether the gingival epithelium is intact or whether a gingivitis is active or even whether it is altered by a prosthetic preparation: the intact crevicular epithelium seems to constitute an effective barrier against the plasmatic passage of adrenaline.

Finally, it should be noted that the various protocols are difficult to compare: duration for inserting the cords varying from 30 to 120 minutes, variable number of teeth concerned, size of the cords and variable doses, non-discrimination of the quantities absorbed by the plasma, the gingival fluid and the saliva.

Pallasch thus suggests keeping some rules concerning the technical specification for research on the tolerance of the cords charged in racemic adrenaline: (1) adrenaline rate actually present on the cord; (2) duration of the presence of the cord in the sulcus; (3) condition of the sulcus; (4) number of teeth concerned; (5) dilution by the saliva and the gingival fluid: (6) metabolism of racemic adrenaline by catechol-o-methyl transferases; (7) local vasoconstriction induced by adrenaline as a factor decreasing its own absorption; (8) gingival traumatism during the insertion of the cords; (9) individual sensitivity of the patient to even minimal variations of the circulating rate of vasoconstrictor.

In the absence of concordant studies, it does not seem possible to formally conclude with respect to the safety of the retraction cords used in dental prosthesis. Studies in animals seem to show that the hemodynamic variations are inconstant, and that their symptomatic nature is dependent either on a sensitivity of the subject, or on the experimental conditions. The literature reports only a single human incident (Hilley, 1984) [Not classified: case] related to the halothane-adrenaline interaction.

1.2.2. *Vasoconstrictors as a means of surgical haemostasis*

Anesthetic substances associated with high amounts of vasoconstrictors were used with the sole objective to control the local bleeding by a broad infiltration of the operational site before incision (Gutman, 1993 [LoP IV]).

Supporters of these techniques nevertheless observe that, on the one hand, it is often difficult to inject near the apexes without infiltrating skeletal muscle fibres rich in adrenergic beta2 receivers which are responsible for a vasodilatation more than for a vasoconstriction (Milam and Giovannitti, 1984 [LoP IV]); on the other hand, this peroperative vasoconstriction is most often followed by a reactive hyperaemia vasodilatation: indeed, progressively with the vasoconstrictor reabsorption, it reaches on the surgical site a concentration which does not ensure any more stimulation of the alpha adrenergic receivers. The blood flow thus finds quickly its normal course then, by rebound phenomenon, progressively reaches a flow higher than normal by beta-adrenergic reaction: this phenomenon is related to the local hypoxia of tissues and the acidosis caused by prolonged vasoconstriction. When this local hyperaemia settles, the complementary LA injections with vasoconstrictor are without effect (Gutman, l993; Gutman and Harrison; 1994 [LoP IV]; Syngcuk and Sivakami, 1997 [LoP IV]).

Adrenaline, noradrenaline, phenyl-adrenaline were used only to control local bleeding in endodontic surgery.

Sommer (1962) [LoP IV] was the first to use various solutions: racemic adrenaline at 1/1,000 and 1/1,500, phenyl-adrenaline at 1/100 and noradrenaline at 1/200, the support always being the gauze; Ingle (1965) [LoP IV] suggested filling the osseous cavity with gauze saturated with a racemic adrenaline solution at 2% for 4 minutes. Grossman (1970) [LoP IV] recommends the use of salivary cotton rollers soaked with adrenaline at 1/100,000 and also suggests the use of cotton pellets charged by a racemic solution of adrenaline at 1.5%.

Only the quantities of adrenaline present on the pellets could be evaluated, the other techniques not offering any standardization. Besner (1972) [LoP IIb] thus was able to demonstrate that on no. 2 pellets we find on average 1.15 mg of racemic adrenaline in the form of hydrochloride. The application of a no. 2 pellet for 4 minutes did not bring about any variation in cardiac frequency in the Besner series, which the author attributes to the local vasoconstriction caused by the adrenaline and which would involve very weak and very slow absorption of the adrenaline itself.

Let us note that beside the pellets charged with adrenaline alone, there also exist on the market pellets charged at the same time with adrenaline and astringent substances such as zinc phenol sulfonate and ferric sulphate. These specialties were not tested in the literature and they are not marketed in France to the working group's knowledge. Local haemostatic techniques using pure vasoconstrictors or mixed with anesthetic or astringent substances have not been the subject of a published evaluation with a satisfactory proof level. Thus, they are empirical. Although largely distributed, they did not give rise to the accident or incident publication in connection with the vasoconstrictors.

1.3. Can vasoconstrictors be associated with general anesthetics (GA) during a general anesthesia in odontostomatology?

Using LA solution associated with a vasoconstrictor for the infiltration of the operating field during a general anesthesia has often been recommended as a means of hemostasis in oral and maxillo-facial surgery (Cantaloube et al., 1991 [LoP IV]). It is a comfortable and bacteriologically safe alternative compared with handling designed to extemporaneously manufacture an adrenaline serum.

The adrenaline serum is traditionally composed of sodium chloride at 9‰; the vasoconstrictor action being obtained by addition of adrenaline in solution at 0.025% i.e., 0.25 mg per ampoule of 1 ml of serum. Under these conditions, the usual amount of adrenaline not to be exceeded will be 0.01 $mg.kg^{-1}$ of the patient's weight.

The use of LA as a vector of the vasoconstrictor besides the advantages of handling mentioned above decreases the analgesia threshold, increases the quality of the pre- and post-op control of the pain like Engquist et al. (1977) [LoP IIa], Hosoda et al. (1991) [LoP Ib], Yuge et al. (1995) [LoP IV] demonstrated for epidural anesthesia and especially Mamiya et al. (1997) [LoP Ib] in oral surgery.

Cantaloube recommends for these infiltrations either lidocaine hydrochloride 1% with adrenaline at 1/100,000 or 2% with adrenaline at 1/80,000, or articaine with adrenaline at 1/200 000 or mepivacaine with noradrenaline at 1/100,000.

Tordoff et al. (1996) [LoP Ib] sought to know if the use of a loco-regional anesthesia before incision under general anesthesia for the avulsion of third mandibular molars decreased the post-op pain. They injected among 36 patients the same quantity of anesthetic lidocaine solution on one side and a saline solution on the other. The circumference of the extracted teeth was civilly injected. The post-op pain was evaluated by a visual analogue scale. No significant difference appeared between the physiological serum injected and the anesthetic.

Mamiya et al. (1997) [LoP Ib] conducted the following experiment on a group of 28 ASA 1 patients having to undergo a sagittal mandibular bilateral osteotomy: the 28 patients were divided into 4 groups. Groups 1 and 2 did not receive a loco-regional mandibular anesthesia and were differentiated by a growing level of the depth of the general anesthesia by inhalation quantified by minimal alveolar concentration (MAC) passant de 1.3 MAC à 1.6 MAC. For groups 3 and the 4 patients received in addition to a bilateral loco-regional mandibular anesthesia, a general anesthesia by local inhalation respectively 1.0 MAC and 1.3 MAC. It should be noted that LA's were identical in the two groups receiving the regional anesthesia: 4 ml of mepivacaine 0.5%.

In both groups 3 and 4, a different vasoconstrictor solution was locally infiltrated (group 3: 8 ml of lidocaine 1 % with 10 µg.ml^{-1} of adrenaline; group 4: 8 ml of propitocaine 3% with 0,03 UI.ml^{-1} of felypressin. The general anesthesia was performed with the following general anesthetics: induction by thiopental (4 mg.kg^{-1}) then maintenance by isoflurane and a mixture of 40% nitrogen and oxygen protoxide. The controls of the hemodynamic effects of the surgery were as follows: blood pressure and heart rate. The sympathetic response was evaluated by plasmatic noradrenaline dosage. Measurements started at the 4th minute after local infiltration and were repeated during various significant surgical times.

The results marked very significant differences between the groups with and without loco-regional anesthesia.

No significant difference was observed between groups 3 and 4. The same results are observed in plasmatic noradrenaline rates which are significantly lower in the groups with loco-regional anesthesia.

Thus, the authors conclude that loco-regional anesthesia infiltrations associated with the infiltration of anesthetic solution mixed with a vasoconstrictor in the operational site are instrumental, on the one hand, in decreasing and preventing the auto-immune endocrine sympathetic response to the surgical aggression which is at the origin of a large part of the post-op pains, on the other hand, in decreasing the depth of the general anesthesia necessary for the procedure performed.

A close experiment was undertaken by Santoro and Marsicano (1998) [LoP IIb], with a different goal: to check generated hemodynamic modifications, this time, by the injection of adrenaline while rendering inoperative the stress factors of the awake state induced by the general anesthesia. The authors infiltrated 7 patients under general anesthesia with a solution of 4 ml of mepivacaine 2% with adrenaline at 1/100,000 in the mandibular foramen. The patients were subjected to oral or maxillo-facial surgical procedures very different in nature. The authors noted the variations of the heart rate and the blood pressure in various significant phases of the procedure.

The authors conclude starting from a very debatable protocol that the variations in the heart rate observed during an LA infiltration with vasoconstrictor under general anesthesia are lower than those observed under local anesthesia in awake state.

The use of an anesthetic solution with a vasoconstrictor added as an agent to decrease the bleeding and to reduce the analgesia threshold among oral surgery patients under general anesthesia, is a practice commonly reported in the literature. Recent experiments conducted in epidural and Spix anesthesia of the mandibular nerve show that this practice is instrumental in decreasing the sympathetic response to the surgical aggression and in decreasing the depth of the general anesthesia necessary.

A restriction must be made with GA volatile halogens (halothane) which should not be used with adrenaline. GA halogens indeed cause a potentiation of the depressor effects of catecholamines on the conduction speed of the Purkinje fibres of the autonomous cardiac system (Camara et al., 2001 [LoP IIb]).

2. CHOOSING THE VASOCONSTRICTOR MOLECULE IN ODONTOSTOMATOLOGY

2.1. Adrenaline versus noradrenaline

The neighbouring adrenaline and adrenergic amines cause the vasoconstriction by stimulating specific membrane receivers of the nonstriated muscles cells of the vessels.

Two main types of adrenergic receptors, $alpha_1$ and $alpha_2$, can initiate the vasoconstriction. Anatomically, $alpha_1$ receivers are located close to the sympathetic nerves which innerve the vessels whereas $alpha_2$ receivers are disseminated in order to more easily respond to circulating catecholamines. The cascade of events going from the receptor stimulation to the vasoconstriction is now well established (Ruffolo et al., 1991[LoP IV]).

Adrenergic receptors are connected to effector enzymes and ionic channels by G proteins, i.e. polypeptides which set the guanosine triphosphate at the instant when these receptors are stimulated by adrenaline. The activation of G proteins set on adrenergic $alpha_1$ receptors causes the opening of the calcic channels of the plasmatic membrane and a C phospholipase stimulation. Calcium ions thus penetrate the cell and activate a kinase of the light chain of the calmoduline-dependent myosin. It is this which, in its turn, initiates the muscular contraction. During this time, the hydrolysis of certain components of the cellular membrane by C phospholipase leads to the formation of diacylglycerol and inositol triphosphate. These second messengers induce the contraction by facilitating the release of the intracellular calcic reserves and by bringing about the activation of the C kinase protein which contributes to the metabolic support of the contraction.
Stimulation by vasoconstrictors of the $alpha_2$ receptors also opens calcic channels by G proteins activation. Moreover adenylcyclase is inhibited by a specific inhibitor G protein.
The $beta_2$ adrenergic receptors activate, on the other hand, the adenylcyclase and consequently bring about a vasodilatation. $Beta_2$ receptors are widespread in the vessels of the skeletal muscles and in certain internal organs, they are rare in the mucosas and in the skin. Noradrenaline shares with adrenaline the capacity to stimulate the $alpha_1$ and $alpha_2$ receptors but it does not interact with the $beta_2$ receptors so that the only direct effect of noradrenaline on the vessels is to promote their constriction.

This purely alpha-adrenergic character was initially profitably employed by industry as a proof of specificity of this catecholamine. In fact, the affinity of noradrenaline for alpha receptors is less than that of adrenaline which implies the use of more significant noradrenaline amounts to obtain the same vasoconstriction (Knoll Kohler. 1988 [NdP IV]).

Noradrenaline is thus about 4 times less locally vasoconstrictor as adrenaline. The first consequence is a shorter action as result of faster plasmatic absorption. The intravascular noradrenaline injection has consequences more severe than those of adrenaline: rise in the systolic blood pressure (> 200 mm Hg), increase from 75 to 80% of the average blood pressure and increase in myocardial consumption of oxygen (Boakes, 1972 and 1973 [LoP IV]) which makes a molecule difficult to handle among patients suffering myocardial ischaemia.

The absence of the noradrenaline action on the $beta_2$ receptors produces an increase in peripheral vascular resistances which largely explains its toxicity. Noradrenaline has moreover a serious and paradoxical bradycardiac action because it is active on the cardiac $beta_1$ receptors; it should logically result in an acceleration in heart rate. In fact, noradrenaline could also cause a reflex stimulation of the aortic and carotidian baroreceptors in response to the rise in the diastolic and systolic pressures and involve an abrupt bradycardia (Berini and Gay, 1997 [LoP IV]).

The duration of the elevation in blood pressure consecutive to the injection of noradrenaline is 4 minutes, and 15 minutes for the bradycardiac effect (Knoll Kohler, 1988 [LoP IV]).

Anesthetic solutions added with an association of adrenaline and noradrenaline were marketed. Although no specific study was published on this subject, the opinion of the literature is unfavourable affirming that the beneficial effects of these associations are not higher than those of adrenaline alone while they add the disadvantages of noradrenaline (Jage, 1993 [LoP IV], Berini and Gay, 1997 [LoP IV]).

2.2. **Other vasoconstrictors**

In front of the risks identified with catecholamines, the researchers and the industrialists thought of using non-catechol vasoconstrictor substances, derived from a natural hormone secreted by the posthypophyse: the vasopressin.

Felypressin (phenyl alanine2-lysine-vasopressine 8) is the leader among synthesis analogues of the vasopressin; it has the local vasoconstrictor characteristics of vasopressin without having the powerful diuretic effects nor the vasoconstrictor effects on the coronary arteries (approximately one-third of the coronary action) (Goldman et al., 1971 [LoP IIb]).
It would not act on the blood pressure nor on the central nervous system (Von Tsakiris and Bultmann, 1961).

A recent and well documented study (Sunada et al., 1996 [LoP IIa]) relativises the systemic advantages of the felypressin which was regarded for a time as the vasoconstrictor of choice among patients with medical history of myocardial ischaemia (Johnson and Widrich, 1977 [LoP Ib]). In this article, the myocardic effects of various solutions of propitocaine at 2% associated with doses varying from 0 (control group) to +0.25UI.ml-^{1} of felypressin are compared among 26 patients suffering from essential hypertension. The results show that the systolic pressure is increased compared to the control for the groups with raised proportioning in felypressin but that all the groups have a rise in the diastolic pressure compared to the control. Even if myocardic ischaemia is not highlighted in a formal way because of experimental skews, the authors observe a reduction of the myocardic contractibility in all 3 groups the most proportioned in felypressin. They conclude by recommending among patients affected by essential hypertension an amount of 0.18 UI felypressin what corresponds to 6 ml of propitocaine at 3 % with 0.03 UI felypressin.

Volpato (1999) |LoP Ib] shows that with raised amount in animals, the toxicity of adrenaline and felypressin are comparable but that adrenaline would have a "protective" effect with respect to the occurrence of convulsions when it is associated with lidocaine.

Shanks (1963) [LoP III] showed that effects from the interaction of felypressin and general halogen anesthetics are close to those of adrenaline. Roberts and Sowray (1987) [LoP IV] recommend not using felypressin in pregnant women because of a possible inhibiting action on placental circulation by interference with uterine tonicity.

Ornipressin (POR-8) is another synthesis analogue of the vasopressin having local vasoconstrictor properties. For a while it was described as a vasoconstrictor of choice in the infiltration of the operating field but serious complications (Kleemann et al., 1986 [LoP IV]; Cantaloube, 1991 [LoP IV]) showed its powerful constrictor effect on the coronary arteries and caused it to be abandoned.
Mixed with an LA ornipressin has much lower performance than adrenaline: it takes approximately 10 minutes to obtain maximum vasoconstrictor (Jage, 1993 [LoP IV]) effect making it difficult to use.
Corbadrine is still found in association with the aptocaine, LA having experienced a return to normal recently due to a good tolerance in some hepatic porphyries. The corbadrine is the alpha-methyl noradrenaline much less toxic than noradrenaline itself. Nevertheless its vasoconstrictor activity is weaker. It is necessary to give 10 times stronger doses of corbadrine to obtain an effect comparable to that of noradrenaline. Moreover, this synthetic substance is slowly eliminated resulting in a prolongation of the action which can constitute an obstacle. This prolongation of the effect duration is related to the presence of the methyl group which prevents the degradation of the corbadrine by the mono-oxidase. (Jacquot et al. 1978 [LoP IV]).

From an industrial and medical point of view, adrenaline is the leader in vasoconstrictors used alone or in association with a local anesthetic in odontostomatology. It uses the broadest case-mix which confirms a high safety for this molecule. The non-catechol derivatives have not proven to date their superiority even among patients likely to not tolerate catecholamines well.

3. INDICATIONS OF VASOCONSTRICTORS IN ODONTOSTOMATOLOGY

Qualities of the vasoconstrictors associated with LA solutions were recalled in this work and justify the very broad use of these associations during infiltration anesthesias in odontostomatology.
The working group questioned regarding two anatomically opposed anesthetic techniques for which the use of vasoconstrictors poses different problems. This refers to:

- on the one hand local anesthesias called casual (intrapulpal, intraseptal, intradiploic and intraligamentary anesthesia) ;

• on the other hand loco-regional anesthesias in the mandibular foramen performed in a richly vascularised territory on the arterial level as well as on the venous level which raises the risk of endovascular injection of an adrenaline anesthetic substance.

3.1. Do vasoconstrictors have to be used during casual anesthesias?

The casual anesthesias have in common the fact that the anesthetic solution is infiltrated in an anatomically closed space where the diffusion will be minimal so that the quantity injected will be weak so that the addition of a vasoconstrictor could appear useless, even harmful, because of the tissue aggressiveness of the local vasoconstriction which it brings about (Madrid et al., 1991 [LoP IV]).

Intraosseous or intradiploic anesthesia has been the subject of many studies aiming to study in particular the contribution of these techniques as a complement for mandibular nerve loco-regional anesthesia techniques in the mandibular foramen. Reitz et al. (1998) [LoP Ib] tested a solution of 0.9 ml of lidocaine 2% with adrenaline at 1/100,000 in intraosseous injection on the 2nd molar, 1st molar and 2nd premolar area on 38 subjects. Guglielmo et al. (1999) [LoP Ib] followed a strictly identical protocol with a solution of mepivacaine 2% added with 1/20,000 levonordefrin on 40 subjects. In both cases no local complications were reported by the authors upon the use of a vasoconstrictor in intraosseous injection. As for Dunbar et al. (1996) [LoP Ib] and Coggins (1996) [LoP IIa], they have noted an inflammation and suppuration at the injection point but in both cases the authors incriminate the perforation technique and not the possible effect of the vasoconstrictor.

As for Replogue et al. (1998) [LoP Ib], he established the superiority of the intraosseous injection of lidocaine 2% with adrenaline at 1/100,000 compared to a solution with mepivacaine 3% without vasoconstrictor during the anesthesia of the 1st mandibular molar what well seems to indicate an interest in the use of vasoconstrictors since mepivacaine is practically neutral for the vasodilatation or even slightly vasoconstrictor. These results are concordant with those of Petrikas (1990) [LoP III], who studied on 22 subjects the effectiveness of a solution of lidocaine with and without adrenaline during a series of intraseptal injections: he concludes that the addition of adrenaline brings an improvement in the depth of the anesthesia, its duration and success rate, is instrumental in the pulpal dissemination of the anesthesia and does not increase the local noxious effects.

For intraligamentary anesthesia, the studies of Tagger et al. (1994) [LoP Ib] clearly showed that the anesthesia results more from intraosseous diffusion than from direct diffusion to the apex so that the remarks made for the intraosseous techniques should apply to the intraligamentary techniques.

In fact, the works of Gray et al. (1990) [LoP IIa] showed at the same time the absence of noxious effects of vasoconstrictors associated with the anesthetic solution injected in intraligamentary (lidocaine + adrenaline or prilocaine + felypressin) and the marked superiority of the success rates with vasoconstrictors compared to LA alone.

The studies of Wallon (1982) [LoP IIb] and Galili et al. (1984) [LoP IIb] show an ad integrum return of the desmodontal ligament after 8 to 15 cicatrisation days in monkeys having undergone intraligamentary injections with solutions comprising a vasoconstrictor. Tsirlis et al. (1992) [LoP IIa] showed on a study group of 305 dental mandibular avulsions that the frequency of the dry alveoli after intraligamentary anesthesia was not increased compared to a control group with traditional anesthetization.

Mc Lean et al. (1992) [LoP Ib] showed the superiority of a solution of bupivacaine with adrenaline at 1/200,000 compared to a solution of lidocaine with adrenaline at 1/100,000.

Finally in a methodological rigorous study, Handler and Albers (1987) [LoP IIb] compared the use during intraligamentary anesthesia for 4 different solutions: lidocaine 2%, lidocaine 2% with adrenaline at 1/50,000, lidocaine 2% with adrenaline at 1/100,000 and finally adrenaline at 1/100,000 alone. Their surprising results show that contrary to what is usually reported, there is no relation of proportionality between the amount of adrenaline present in the solution and the duration of the anesthesia measured by pulp tester. There is no difference between the 4 solutions as for the anesthesia success frequency.

The anesthesia is also obtained with a solution of adrenaline alone which the authors explain by the fact that the anesthesia would here be related to the pressure and not to the pharmacological action of the vasoconstrictor.

The use of a vasoconstrictor in casual anesthesia techniques is not essential but considerably improves the success rate, duration and depth of the anesthesia obtained. If the injection is performed under the proper conditions: controlled pressure, slow injection, small volumes -on average 0.2 ml per dental root, (Handler and Albers, 1987) [LoP IIb]-, local lesions directly ascribable to the vasoconstrictor are negligible and reversible. There are systemic effects of these injections but they are most often much lower than those observed in infiltration anesthesias.

3.2. **Do vasoconstrictors have to be used during loco-regional anesthesias of the mandibular nerve?**

For a long time the risk of an intravascular injection of adrenaline anesthetic solution was advanced as an argument in favour of disregarding the use of a vasoconstrictor in the anesthesia technique of the mandibular foramen (Gaudy and Aretto, 1999) [LoP IV]).

This argument is opposed to the consensual feeling in the profession that the success rate of the loco-regional mandibular anesthesia is related to the presence and the dose of the vasoconstrictor. The literature does not confirm this impression.

Keesling and Hinds (1963) [LoP Ib] compared 5 solutions of lidocaine 2% with adrenaline respectively at 1/50,000, 1/250,000, 1/750,000, 1/1,000,000 and without adrenaline for mandibular foramen anesthesia. Authors report a success rate by pulp tester of 87.5% for an average anesthesia duration of 44 ± 5.7 minutes for lidocaine without adrenaline. To be compared for example with a success rate of 96% and an average duration of 66.9 ± 8.7 minutes for the solution at 1/750,000. No significant difference seems to exist between the solutions at 1/50 000 and 1/250 000, neither for the success rate, nor for the duration of the anesthesia.

Mac Lean et al. (1993) [LoP Ib] thus showed by testing 3 anesthetic solutions on 30 subjects (lidocaine 2% with adrenaline at 1/100,000, prilocaine 4% alone and mepivacaine 3% alone) that there was no significant difference regarding the success rates of the anesthesia of the mandibular foramen controlled by pulp tester.

Dagher et al. (1997) [LoP IIa] tested 3 solutions of lidocaine 2% with adrenaline respectively at 1/50,000, 1/80,000 and 1/100,000. According to MacLean's methodology (1993) on 30 subjects in good health, the 3 solutions appear equivalent for success rate, failure rate and anesthesia frequency.

Malamed (1997) [LoP IV] recommends Spix anesthesia of the inferior alveolar nerve with vasoconstrictor only in the case when a prolonged anesthesia duration is required. Knoll-Kohler and Fortsch (1992) [LoP Ib] tested, on 10 students, two solutions of lidocaine at 2% without adrenaline, one having pH 3.5, the other having pH 6.8, and three solutions of lidocaine 2% with adrenaline at 1/50,000, 1/100,000 and 1/200,000. According to these authors the lidocaine without adrenaline, whatever the pH may be, shows a high rate of failures and a weaker duration. The addition of adrenaline at 1/100,000 or 1/200,000 improves the success rate and the duration of the anesthesia but does not vary the latency time. These results are in agreement with those of Kabambe et al. (1982) [LoP Ib] who observe, comparing a solution of lidocaine with and without adrenaline, a failure in more than half of their subjects for the anesthesia of the inferior alveolar nerve.

The addition of a vasoconstrictor to the anesthetic solution is not essential for the anesthesia of the mandibular foramen of the inferior alveolar nerve. The addition of adrenaline increases the duration of the anesthesia but does not seem to have a decisive effect on the success rate. The results concerning the success rate of the anesthesia are contradictory. Taking into account the relation that exists between the success rate and the volume of the solution injected (Vreeland, 1989) [LoP IIb], the addition of a vasoconstrictor could be considered in the prevention of systemic effects of LAs.

Another argument called upon to dispute the use of a vasoconstrictor in loco-regional anesthesia of the mandibular nerve is the fact that the vasoconstrictor could lengthen the duration of the labiomental anesthesia and consequently wounds from labial self-bites which constitute one of the most frequent adverse effects of these injections (Wahl, 2000). In fact, works showed that only the pulpal anesthesia is lengthened during loco-regional anesthesias of the mandibular nerve with vasoconstrictor and not labiomental anesthesia (Hersh and Hermann, 1995 [Not classified: clinical case];Yaguiela, 1985 [LoP Ib]).

4. DOSAGE OF VASOCONSTRICTORS IN ODONTOSTOMATOLOGIC ANESTHESIA

No definitive conclusive studies exist concerning ideal LA proportioning in adrenaline.

Fink (1978) [LoP IIb] showed that the duration of the local anesthesia (all techniques included) was directly dependent on the amount of adrenaline present in the solution: the duration obtained for a lidocaine 1% solution with adrenaline at 1/50,000 is 210 minutes, 160 minutes at 1/100,000 and 130 minutes at 1/200,000. Taking into account the average duration of the dental procedures Himuro et al. (1989) suggest replacing lidocaine at 1/80,000 by lidocaine at 1/200,000 after a comparative test on only 6 volunteers. Since 1967, Gangarosa and Halik [LoP Ib] showed that the 1/100,000 or 1/300,000 lidocaine solution were equivalent for installation speed and the effectiveness evaluated according to the experiment of a group of 17 dental surgeons during a prospective double blind series of 542 patients. Regarding the duration of the anesthesia, which we assess since Braun (1924) [LoP III] that it is dose-dependent, the results of the same study show a negligible gain in terms of duration while going from the anesthetic solution with adrenaline at 1/300,000 to 1/100,000. Knoll-Kohler (1992) [NP Ib] after a study on 10 volunteers affirms that only lidocaine at 1/100,000 gives consistent results.

Obviously, the doses of adrenaline must be adapted to the characteristics of the LA molecule. Apart from lidocaine, the market is occupied by carticaine or articaine which is marketed with added adrenaline at 1/100,000 and 1/200,000.
Vahatalo et al. (1993) [LoP Ib] tested the lidocaine 2% with adrenaline at 1/80,000 and articaine 4% with adrenaline at 1/200,000 for the latency time and the duration of the anesthesia controlled by pulp tester. There was no statistically significant difference between the two groups what would make it possible to choose the least adrenaline-proportioned molecule. Knoll-Kohler et al. (1992) [LoP Ib] compared articaine 4% at 1/100,000 and the solution at 1/200,000 during a 3rd impacted mandibular molar avulsion by measuring the variations of the heart rate, the concentration of cyclic AMP and the noradrenaline rate. These parameters were correlated with the plasmatic rates of adrenaline as an indicator of the endogenous secretion.

Adrenaline reabsorption from the injection site turned out to be dose dependent, which should have made lead the authors in favour of the solution at 1/200,000 adrenaline. In fact, in a previous study, Knoll-Kohler (1991) [LoP Ib] estimated that the risk of cardiovascular incident was particularly higher when the operational gesture was prolonged and proportioning in adrenaline was weak.
This result is disputed by the studies of Daublander et al. (1997) [LoP III] which note that the sympathicomimetic side effects of the LA injections with vasoconstrictor are significantly higher in their retrospective series of more than 2,700 subjects for the 1/100,000 articaine solution in comparison with the 1/200,000 articaine solution.
Jage (1993) [LoP IV] estimates that the best concentration for the healthy patient is (all molecules included) from 1/100,000 to 1/200,000 knowing that the individual maximum dose is 0.25 mg. On the other hand for the patient presenting a vascular affection the obligatory concentration would be 1/200,000. Let us remember that for 1 ml of anesthetic solution, a 1/1,000 solution represents 1,000 µg of adrenaline while a 1/200,000 solution contains 5 µg of adrenaline.

For mepivacaine Berling's studies (1958) [LoP IIb] show an absence of statistically significant difference between the adrenaline 2% solutions respectively at 1/100,000 and 1/200,000 for the success rate and the duration of the pulpal anesthesia.
The studies are also contradictory concerning the ideal dosage of adrenaline in lidocaine 2% solutions. The solution at 1/200,000 gives more than two hours of anesthesia which represents a sufficient duration for the vast majority of odontostomatologic procedures. For articaine at 4% and mepivacaine at 2%, solutions at 1/200,000 should be preferred in the absence of significant difference in performance with the solution at 1/100,000.

Finally Jorkjend and Skoglung's studies (2000) [LoP Ib] clearly show:
- on the one hand that the increase in the volume of adrenaline and the local anesthetic solution injected can have an adverse effect which is the increase in the post-op pain without counterparts in terms of duration or quality of the anesthesia;
- on the other hand the increase in the adrenaline proportioning in the anesthetic solution also significantly increases the post-op pain by elevating the rate of cyclic AMP in gingival tissues which promotes the accumulation of nociceptive substances or pro-algesic mediators.

5. Drug interactions

The vasoconstrictors employed in association with LA but also like haemostatic or injectable topics and finally on the gingival retraction cords have the potential to interact with a broad variety of drugs (Hansten, 1981) [LoP IV].

The local reactions go until local ischaemia and to necroses (Yagiela, 1999; Damm and Fantasia, 1992). They are related to the relative overdose by saturation of tissues with vasoconstrictor and to the too fast injection (Meechan, 1998).

Most of the systemic reactions are of short duration mainly because of the rapid inactivation of the vasoconstrictors once they are absorbed in the blood flow (Yaguiela, 1999) [LoP IV]. Nevertheless serious lesions even death of the patient can result from a fibrillation of drug origin, of a myocardial infarction or of a cerebra-vascular accident (Hilley, 1984; Okada, 1989; Massalha, 1996) [Not classified: clinical cases].

5.1. Tricyclic Antidepressants

They are progressively replaced by selective serotonin reuptake inhibitors. They nevertheless remain used among patients intolerant or resistant to these new drugs.

Tricyclic antidepressants block the active reuptake of biogenic amino neuro-transmitters (catecholamines and serotonins) by the nerve endings where they were salted out. The result is a potentiation of the neuro-transmitters concerned: adrenergic vasoconstrictors but especially noradrenaline are subject to the same reuptake phenomenon. Tricyclic antidepressants block the muscarinic receivers and alpha 1 adrenergics and depress the myocardium which can modify in return the cardiovascular response to the vasoconstrictors.
According to Boakes et al. (1972) [LoP IV] out of 15 cases of patients presenting severe problems with noradrenaline, 5 took tricyclic antidepressants.

Such accidents can occur with injections of 2.5 cartridges of 1/100,000 adrenaline (Persson and Siwers, 1975) [LoP IV].

Cawson et al. (1983) [LoP IV] disregarded the possibility of clinically significant interactions between tricyclic antidepressants and LA containing adrenaline.

In reality if the theoretical risk is high the clinical signs are rare. Several factors contribute to this:
- the competition between the vasoconstrictor (a-adrenergic) and vasodilator (ß2-adrenergic) effect leads to a compensation for the hemodynamic variations in the usual doses in odontostomatology;
- prescribing these drugs often is done on long course what causes a desensitization to the adrenergic vasoconstrictors and consequently a reduction in the risk of interaction (Moyer et al., 1979) [LoP Ib].

The attitude towards patients under tricyclic antidepressants must be to disregard noradrenaline in association with local anesthetics and to inject reduced amounts of local anesthetics associated with adrenaline at 1/100,000 or 1/200,000. In practice the amount injected should be one-third of the total amount for the normal subject (Yaguiela, 1999 [LoP IV]).

5.2. Monoamine oxidase inhibitors

Selective inhibitors still used alone do not present an interaction with adrenaline. Repeated studies in humans and animals did not show any significant interaction with the amounts used in odontostomatology (Boakes et al., 1973 [LoP IV] ; Wong et al., 1980 [LoP Ib]).

5.3. Beta blockers

Although broncho and vasoconstrictor effects can theoretically appear during the administration of selective cardio or $beta_1$ beta-blockers (which are thus likely to bring about asthma attacks), no incident has been described among patients among whom cardio-selective beta-blockers and an adrenaline anesthetic solution were associated (Pallash, 1998 [LoP IV]).

It is thus mainly non-cardio-selective beta-blockers that block in a competing manner the stimulation of the $béta_1$ and $béta_2$ receptors by endogenous catecholamines which are in question. They also block the activation of beta receptors by exogenous catecholamines. It is mainly on the level of the $beta_2$ receptors that the beta-blockers are going to act in converting adrenaline into an exclusively alpha-adrenergic drug.

The consequences are an increase in peripheral resistances and, in directly connection with the amount, an increase in the blood pressure and a deceleration of the heart rate which can lead to major and well documented accidents (Hansbrough and Near, 1980; Foster and Aston, 1983 [Not classified: clinical cases]).
This risk must be tempered for non-cardio-selective beta-blockers with intrinsic sympathomimetic activity (ASI) for which the partial beta-agonist activity leads to a limitation of the bradycardial and vasoconstrictor effect. Let us note that local beneficial effects were described for beta-blockers as extending the duration of the pulpal and soft tissue anesthesias (Zhang, 1999 [LoP Ib]). The precautions will include a fractioned and slow injection of LA added with adrenaline at a maximum of 1/100,000 after negative aspiration.

5.4. General Anesthetics

We have seen the possible interactions with the halogen derivatives.
The mechanism by which GA potentiate the arrythmogenic effects of catecholamines are unknown. They are probably a simultaneous stimulation of the $alpha_1$ and beta receptors. Adrenaline is in its own right able to activate the two types of receptors and to generate disorders of the rate during general anesthesia (Hayashi, 1993 [LoP Ib]). The thiopental is also able to exaggerate the arrythmogenic potential of the adrenergic substances. Being given that the thiopental is often used in the induction of halogen derivatives, its interaction was initially under-estimated. When the thiopental is used alone, a dose of 2 $\mu g.kg^{-1}$ adrenaline will be allowed in peroperative injection under general anesthesia. This dose will be 1 $\mu g.kg^{-1}$ if the thiopental is associated with halothane (Christensen et al., 1993 [LoP IV]). We reported one death under halothane, due to an interaction with a retraction cord with racemic adrenaline (Hilley et al. 1984 [Not classified: clinical case]).

5.5. Cocaine

Experiments in the animal and human cases brought the proof of cocaine interaction with adrenergic vasoconstrictors. (Lathers et al., 1988) [Not classified: clinical case].

Several deaths for which study is well documented, appear in the literature (Chiu, 1986) [Not classified: clinical case]. The mechanism is a facilitator effect of cocaine on the salting out of the adrenergic neuro-transmitters and the intensification of the post-synaptic responses to adrenaline-mimetic substances. The blocking of the cardiac muscarinic receptors and the central deterioration of the autonomic nervous system can moreover play a part in worsening the reactions to the injection of vasoconstrictors.

No dental treatment should be performed for a patient under the influence of narcotics. Vasoconstrictors will be barred at least 24 hours after the consumption of cocaine to allow the elimination of the drug and its active metabolites.

5.6. Antipsychotics and alpha-blockers

These drugs (chlorpromazine, thioridazine, risperidone) have as a side effect of blocking the alpha-adrenergic receptors and thus causing orthostatic hypotension reactions. In case of overdose, the plasmatic passage of adrenaline would be worsening since only the $beta_2$ receptors would be activated bringing about a vasodilatation. It is in fact a strictly theoretical risk: no seriously documented accident was reported at the amounts used in odontostomatology.

5.7. Guanethidine

As a substance inhibiting the salting out of the noradrenaline on the sympathetic terminal nerve fibres, it is used in the treatment of severe arterial hypertension: used over the long-term it could cause a multiplication of the adrenergic receptors or a decrease in their sensitivity threshold. This risk is theoretical for a rare drug.

5.8. Adrenergic anorexiants

There are sympathomimetic drugs affecting the metabolism of catecholamines and are chemically close to the amphetamines. These drugs increase the adrenergic neurotransmission and stimulate the central nervous system, their anorexigenic activity stems from this stimulation of the CNS. Their effects can be potentiated by the concomitant use of vasoconstrictor substances.

This is the case of mazindol for which the FDA and the manufacturer recommend precautions of use with the vasoconstrictors (Wynn, 1997 [LoP IV]).

6. DO PATHOLOGIES EXIST CONTRA-INDICATING THE VASOCONSTRICTORS?

We must keep in mind that 45% of the consultants in the dental office have one or more pathologies intercurrent with the oral-dental pathology and that 20% of them have a cardiovascular disorder. Daublander et al. (1997) [LoP III] estimate in their series at 0.07% the risk of serious accident in connection with the local anesthesia in the dental office which is consistent with the incidence of serious complications from general anesthesia (0.05 %). But these figures must be balanced by the status of the patient. Thus the side effects observed under dental local anesthesia concern 5.7 % of patients at risk against 3.5% of healthy patients. These figures are to be reconciled with those of general anesthesia for which the side effects affect 12.3% of ASA I patients and 34.9% of ASA III and IV patients. Daublander clearly shows that the side effects measured are independent from the anesthetic molecule used (articaine, lidocaine or mepivacaine) and the presence or not of an associated vasoconstrictor but rather depend on the dosage used.
The local anesthesia with vasoconstrictor is thus, in odontostomatology, a very safe technique whose contra-indications appear largely exaggerated.

6.1. Hyperthyroidism

Hyperthyroidism can result from a disease or stem from a chronic overdose in thyroxine. Hyperthyroidism will result in cardiovascular disorders which reproduce the effects of an overdose in adrenaline: tachycardia and other arrhythmias, widening of the amplitude of the pulse, myocardial ischaemia, etc. For a long time, it was believed that adrenaline and noradrenaline took part in hyperthyroid disorders in a synergistic way with the thyroxine. It is nothing of this: in the case of hyperthyroidism, the hemodynamic responses to the adrenaline and noradrenaline action are not basically changed. (Yaguiela, 1999 [LoP IV]).

Recent studies (Johnson, 1995 [LoP Ib]) showed that hyper and hypothyroid patients do not have major disorders when they are subjected to a corrective treatment and put in contact with catecholamines at a distance at the beginning of this treatment.

Although the theoretic risk of thyroxine-adrenaline potentiation is serious, there are no reported clinical cases.

6.2. Hypertension

Hypertension and its relation with vasoconstrictors are the subject of an abundant literature. It is now largely accepted that the plasmatic passage of the vasoconstrictor is practically negligible in terms of cardiovascular effect (increase in heart rate and blood pressure) in comparison to the secretion of endogenous catecholamines upon pain and stress. The whole debate on the cardiovascular changes induced by the possible addition of one local anesthetic vasoconstrictor is thus based on the evaluation of the exogenous contribution (about twenty $\mu g\text{-}l^{-1}$) caused by a carpule injection in comparison with the current plasmatic rate which is around 300 $\mu g\text{-}l^{-1}$. If we wonder about the physiological capacity to absorb such an exogenous contribution, certain well documented facts can be taken into account: during childbirth without an epidural labour pains can multiply by a factor from 4 to 6 the rate of plasmatic adrenaline (Bonica, 1999 [LoP IV]); during a dental extraction the only stress without pain multiplies plasmatic adrenaline by a factor 10 or 20. The plasmatic passage of 2.2 ml of lidocaine with adrenaline at 1/100,000 during the reabsorption causes only a double rate of plasmatic adrenaline (Tolas, 1982 [LoP IIa]).

Chernow et al. (1983) [LoP Ib] compare the LA injection associated with adrenaline and without vasoconstrictor on 14 healthy subjects for variations in blood pressure, heart rate and the proportioning of endogenous catecholamines. They concern the significant results after injection of the adrenaline solution for the increase in the catecholamine rate for 60 minutes after injection: the rate went from $27 \pm 4\ \mu g.l^{-1}$ to $94 \pm 13\ \mu g.l^{-1}$ in a 1 to 3 ratio. The same team (Cioffi, 1985 [LoP IIb]) reports an increase in a report from 1 to 3.5 in the rate of circulating catecholamines after adrenaline anesthesia for conservative care. These rates being divided by two at the start of a treatment procedure (dam insertion).

In 1993, Lipp et al. [LoP Ib] try to isolate, in the increase of catecholamines that follows an anesthetic injection, the part that results from the exogenous contribution by the anesthetic solution with vasoconstrictor on the part which results from the rise in endogenous catecholamines related to stress from the infiltration and the overall fear of the operating procedure. For this, the authors use an injection of articaine at 4% added with 20 µg of marked adrenaline. They observe a rise in the total adrenaline (exogenous and endogenous) from 5 to 10 times higher compared to the control group treated without anesthesia. They also observe two serum peaks of adrenaline: one 5 minutes after the start of the injection, the other after the start of the dental treatment. The authors affirm that the increase in total catecholamines is mainly the reflection of the exogenous contribution and explain the peak which marks the beginning of the care by the increase in the rate of the plasmatic reabsorption of the anesthetic related to the inevitable massage of the injection site by operator's fingers.

Niwa et al. (2000) [LoP Ib] in a particularly detailed and sophisticated work established that the infiltration of 3.6 ml of lidocaine 2% with adrenaline at 1/80,000 was equivalent, in terms of hemodynamic effects and plasmatic catecholamine rates, to the perfusion of 10 ng.kg.mn^{-1} of adrenaline alone. The plasmatic rate of catecholamines going from 52 ± 24 pg.l^{-1} to 363 ± 105 pg.l^{-1} for adrenaline anesthetic infiltration and from 32 ± 18 pg.l^{-1} to 214 ± 69pg.l^{-1} for the perfusion of 10 ng.kg.min^{-1}, i.e. being multiplied by a factor 7.

But if it could show a significant increase in total catecholamines after LA injection with vasoconstrictor and even show the dominant share of exogenous catecholamines in this increase, it is impossible to accurately know the cardiovascular repercussion of this increase as other added factors render the interpretation of the results randomized.

Thus, Di Angelis and Luepker (1983) [LoP IIa] showed that the only fact of going to the dentist for a simple control caused a rise in blood pressure greater than 4.5 mm Hg compared to an ordinary visit to a doctor. The studies of Gortzack et al. (1992) [LoP Ib] confirm these results and show that there is no difference between normo and hypertensive subjects on this point.

Many authors finally think that it is impossible to establish a proportionality link between increase in total catecholamines and cardiovascular effects, since if most observe this increase after LA injection with vasoconstrictor. They agree not to observe of manifest clinical repercussion in healthy or hypertensive subjects (Sack and Kleeman, 1992 [LoP IIa]).

For their part, Cheraskin et al. (1958) [LoP Ib] have shown that the essence of the rise in blood pressure took place in the waiting room and not in operating phase. This rise in blood pressure was not significantly different between normo and hypertensive but it was significantly reduced in the hypertensive subjects who received a premedication sedative 45 minutes before the appointment time. This work thus clearly highlighted the role of stress compared to the minor role of the injection of exogenous catecholamines during the LA.

The same authors showed during later studies (Cheraskin and Prasertsuntarasai, 1959 [LoP Ib]) that the phase of the 5 to 10 minutes following the anesthetic injection with or without adrenaline is marked by no significant change in the blood pressure or pulse, if the patient is initially normo or hypertensive. They announce Campbell's later results (1996) [LoP IIb] specifying that it is at the beginning and at the end of the operating procedure itself when the most significant changes are observed. Their conclusion is that for the hypertensive patient the use of a preoperative sedative and a vasoconstrictor associated with the LA gives results significantly higher in term of control of the blood pressure and pulse compared with a hypertensive who receives neither sedative nor vasoconstrictor. This result is to be reconciled with Goldstein's studies (1982) [LoP Ib] that show that the hemodynamic variations observed are mainly due to the endogenous noradrenaline secretions under the effect of the operational stress, secretion well compensated by the administration of a premedication sedative by diazepam.

Meyer (1987) [LoP Ib] compared the variations of the blood pressure in 60 healthy subjects receiving for 30 of them an LA adrenaline injection and for the 30 others an LA injection without vasoconstrictor. The results show that the blood pressure of the patients from the group without vasoconstrictor are significantly worse, in terms of monitoring blood pressure, than those of the group with. The author logically explains these results by the bad quality of the anesthesia obtained when LA was injected alone and thus by the endogenous catecholamine hyper secretion.

It should be noted that in the two groups half of the subjects underwent only the anesthesia while the others were subjected to an anesthesia followed by a dental avulsion. In the group without vasoconstrictor, those which underwent the avulsion presented significant variations in blood pressure.

There is thus no contra-indication for using an LA associated with adrenaline in particular for acts requiring a local prolonged and deep anesthesia in a hypertensive subject stabilized by antihypertensor treatment.

The maximum amounts recommended are 0.04 mg in total which corresponds to 2 4.4 ml LA cartridges with adrenaline at 1/100,000. (Budenz, 2000 [LoP IV]).

For the large majority of balanced hypertensives, it will be possible to exceed this limit taking into account the rules of overdose (Meechan, 1998 [LoP Ib]). Among patients with unbalanced pressure, it will be able to continue the anesthesia beyond the two adrenaline cartridges with an anesthetic without vasoconstrictor. Massalha et al. (1996) [Not classified: clinical case] reported 2 cases of intracerebral haemorrhages having resulted in the death of the patient during dental care. We quote them for memory. They are conducting a review of the literature and put, like the majority of the authors, these major hypertensive shocks leading to death on behalf of a hyper stimulation of the trigeminal nerve. The trigeminal ganglion, indeed, in addition to the sensitivity of the face and masticatory motricity, ensures the vasomotor innervations of all the cerebral blood vessels (Moskovitz, 1984 [NdP IV]). They conclude with a simultaneous effect of this hyper stimulation and hemodynamic changes pulled by the rise in the serum peak of catecholamines after anesthetic injection. Their point of view is purely conjectural.

In case of pressure instability associated with other elements encumbering the prognosis, care must be conducted in a hospital environment having a rehabilitation structure and performed under monitoring.

6.3. Heart rate problems

The literature concerning the study of the heart rate variations brought about by the injection of an LA with vasoconstrictor is rich and often of a very good level of proof (Meyer, 1987 [LoP Ih]: Montebugnoli, 1990 [LoP Ib]; Blinder, 1996 [LoP IIb]; Campbell. 1996 [LoP IIb]; Replogue, 1999 [LoP Ib]).

A very well documented study of Campbell et al. (1996) [LoP IIb] made it possible to study the heart rate variations in a population of 40 elderly subjects (20 control subjects and 20 arrhythmic subjects (treated or not)) at various times in the procedure: preoperative, anesthetic injection, peroperative, postoperative. The results made it possible to bring down some truisms: (1) there was no significant difference between the control group and the arrhythmic group for the installation of an episode of benign arrhythmia (17 subjects); (2) the results show in a paradoxical way that the rise in the heart rate is definitely lower during the anesthetic injection compared with the pre and peroperative elevation of the heart rate: (3) the authors demonstrate moreover that the injection of anesthetic solution with vasoconstrictor is probably not involved in the episodes of observed benign arrhythmia: the serum peak of the vasoconstrictor was attained on average 5 minutes after the injection whereas the arrhythmia episodes were at half of the surgical time, i.e. at distance of the vasoconstrictor serum peak. This work is to be reconciled with the results of Blinder et al. (1996) [LoP IIb] results on electrocardiographic changes observed by Holter among 40 cardiac patients monitored 1 hour before an avulsion under LA without vasoconstrictor and 23 hours after. These results show that 14 patients presented significant changes in the ECG and 12 of them an arrhythmia while at the same time no vasoconstrictor was present in the solution.

Another result is that 12 of the 14 patients having presented a significant change in the ECG were under digoxine, either for ischemic accidents or for auricular fibrillation. These results seem to show that capacity of anesthetic injection alone to cause, via physiological and psychological stress associated to injection and via interaction of the pro-arythmogen effects of LA, acute modifications of the heart rate for a significant percentage of patients who are healthy or not in cardiovascular concern (Malamed, 1996).

The authors joined by Stanley Malamed [LoP IV] recommend the monitorisation of patients under digoxine during a local anesthesia. Intraosseous injections which cause a more important rise in heart rate and blood pressure must be avoided (Chamberlain, 2000 [LoP IIb]), Replogue et al. (1999).

[LoP Ib] suggest the use of a solution with mepivacaine 3 % as an alternative to the injection of an adrenaline LA solution among these patients. The rate disorders encountered in current practice are essentially auricular fibrillations balanced by an adapted treatment (Anguera Camos and Brugada Terradellas, 2000 [LoP IV]). Under these conditions the control of the stress and therapeutic heart rate is essential and the use of anesthetic with: vasoconstrictors is indicated. The rules of dosage are the same as previously.

6.4. Coronary Cardiopathies

This pathology is frequently related to the two preceding ones and it appears obvious that close answers can be addressed, nevertheless taking into account the extreme frequency of this pathology and the existing confusion in the spirit on this subject as well for general practitioners or specialists as for the dental surgeons, the working group considered to devote to this point a specific paragraph. . Occasional myocardial ischaemia during known stable or unstable coronary heart disease go clinically undetected in more than 2/3 of the cases (Quyyumi et al., 1985 [LoP IIa]). The extracardial surgery, even minor, is one of the identified sources of episodes of myocardial ischaemia in known coronary patients (Deanfield, 1984 [LoP IIa]). Many studies have shown that the anomalies of the ST segment of the ECG translate episodes of myocardial ischaemia. In 1989, Vanderheyden et al. [LoP Ib] studied these anomalies of the ST segment during periodontal care under LA with vasoconstrictor among known and treated coronary patients, placed under monitoring in order to evaluate the anomalies of the ST segment in the phase immediately following the LA injection. They show that the use of LA with vasoconstrictor does not cause any significant modification of the ST segment taken as indicator of a myocardial ischaemia. The American Dental Association and American Heart Association's recommendations (1984) specify that the vasoconstrictors are not contraindicated in these affections when a safe anesthetic technique is used, when an aspiration test is conducted and when the smallest effective amount is used.

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6.5. Asthma

Vasoconstrictors associated with an anesthetic solution are not contra-indicated for asthmatic subjects designed to monitor the pain and to avoid the stress which is probably the main trigger source for an asthma attack in the dental office.

Adrenaline alone is used furthermore for its broncho-dilating properties in the treatment of asthma and a recent systematic review reports level 3 and 4 clinical studies that confirm the absence of adverse effects during this use (Safdar et al. 2001 [LoP IV]). In the particular case of cortico-dependent asthma (Bush and Taylor, 1986 [LoP IIb]; Perusse et al. 1992, 2 [LoP IV] the difficulty of over-sensitiveness to sulphites, vasoconstrictor's conservative, can arise. It seems however that 96% of asthmatics are not sensitive to the metabisulfite in question (Send, 1986). In addition, Wahl (2000) makes the observation that a meal at a restaurant contains on average from 25 to 200 mg sulphite i.e. 27 times the amount contained in one cartridge of lidocaine with adrenaline at 1/100,000 (0.9 mg). The recourse to an anesthetic without vasoconstrictor and bisulfite is however indicated in the case of cortico-dependent asthma.

6.6. Hepatic insufficiency

Patients having presented an old and cured viral or toxic hepatic attack can be treated as healthy patients. In case of severe evolutive attack, the assessment of the liver damage is important. The total quantity injected may have to be reduced and the intervals between the injections increased, without prejudice to the use of an associated vasoconstrictor.

6.7. Diabetes

Among balanced type I or II diabetic patients, the use of vasoconstrictors is indicated. In case of unbalanced and unstable diabetes, abruptly going from hypo to hyperglycaemia, the quantities of local anesthetic with vasoconstrictor will be moderate so as to take into account the hyperglycaemic character of the adrenaline (Meechan, 1996 [LoP Ib]).

6.8. Pheochromocytoma

It is a tumour of the adrenal medulla or of the sympathetic paravertebral ganglion which causes a severe hypertension as result of endogenous hyper secretion of adrenaline. Because of the risk of cardiovascular disorders potentiation, the pheochromocytoma and all the tumours of the adrenal medulla constitute an absolute contra-indication for vasoconstrictors (Kaufman et al., 2002 [LoP IV]; Gaudy and Arreto, 1999 [LoP IV]; Perusse et al., 1992 [LoP IV]).

The injection of anesthetic solution without vasoconstrictor when it is necessary in the patient affected by a pheochromocytoma must take place in hospital environment and under monitoring taking into account the difficulties of blood pressure peroperative stabilization among these patients (Niruthisard et al., 2002 [LoP III]; Tanaka et al., 1991 [LoP III]; Pratilas and Pratila, 1979 [LoP IV]).

6.9. Irradiated bone

Any irradiation of the maxillo-facial structures with a therapeutic purpose that it is in the form of brachy or remote radiotherapy reduces bone vascularisation so that the bone tissue is no longer able to defend itself against aggressions. An oedema followed by endothelial necroses involves successively the hyalinization, the fibrosis and thrombosis within the wall of the irradiated vessels. The vessels are obliterated and tissue hypoxia leads to the lysis of collagen then to a degeneration of medullar osseous (Marx, 1983 [LoP III]). It is the osteoradionecrosis (ORN) or radiation osteitis which constitutes one of the major complications of maxillo-facial therapeutic irradiations.

It is easily understood that such a process which generally occurs with irradiations higher than 60 Gy can be promoted by the local ischaemia caused at the point of injection of an LA mixed with vasoconstrictor.

In animals Heiss and Grasser (1968) [LoP Ib] showed under extreme experimental conditions the significant increase in the risk of ORN after injection of vasoconstrictor substances in contact with mandibles of irradiated rats. Obviously, there does not exist a comparable protocol for humans. On the other hand, Maximiw et al. 1991 [LoP IIb] showed that the use of low doses of vasoconstrictors or LA solutions without vasoconstrictor succeeded, for a group of 449 avulsions performed in a bone having received on average 50 Gy (extreme at 25 and 84 Gy), in a total absence of post-extraction osteoradionecrosis and this after a post-extraction follow-up of 4.8 years on average.

Although the clearly identified risk factors of the post-extraction ORNs are the mandibular site, the total amount delivered and the mode of irradiation (Curi and Dib, 1997 [LoP III] and that there is not any evaluation of the direct risk related to vasoconstrictors in humans; it appears desirable to avoid the association of vasoconstrictors to LA during conservative care and especially non-conservative care on a bone irradiated beyond 40 Gy.

7 PHYSIOLOGICAL CONDITIONS AND VASOCONSTRICTORS

7.1. Pregnancy and lactation

Although vasoconstrictors (especially noradrenaline) have a reduction potential of the placental perfusion, the studies conducted on this subject have not shown any adverse effect for adrenaline on the foetus (Haas et al., 2000 [LoP III]. In reality, the amounts of adrenaline used in the marketed local anesthetic solutions are so weak that it is very improbable that they can affect the uterine blood flow. Regarding lactation, the only available data are the opinion of the authors. They confirm the possibility of using vasoconstrictors in association with LA for woman currently breast feeding (Gibbs and Hawkins, 1994 [LoP IV]; Malamed, 1997 [LoP IV).

7.2. The child

In the child, the assumption of responsibility for the pain is traditionally done by avoiding a systematic recourse to the vasoconstrictors. This practice has no relationship with the toxic risk. It rises from the increase in the severe labial bite risk of the anaesthetized area for a long time after the end of the treatment due of the extension of the anesthesia duration in the presence of a vasoconstrictor (Walh, 1997 [LoP IV]; Gaudy and Aretto, 1999 [LoP IV]). That mainly concerns loco-regional anesthesia of the mandibular nerve and the danger of biting the lower lip.
Hersh and Hermann (1995) [LoP Ib] nevertheless showed that there was no significant difference in the duration of labiomental anesthesia after injecting mepivacaine without vasoconstrictor when we compare it with an injection of lidocaine+adrenaline. According to these authors, resorting to an anesthetic without vasoconstrictor in the child is thus not interesting and they recommend on the contrary the use of the lidocaine 2% with adrenaline until a total amount of 4.4 1.8 ml carpules in a 25 kg child versus 2.8 cartridges of mepivacaine 3% without adrenaline.

Let us note that Hersh et al. (1991) [Not classified: clinical case] brought back a fatal overdose in a 5-year-old child weighing 16.4 kg and in whom had been injected 5 1.8 ml cartridges of mepivacaine 3% without vasoconstrictor.

There are various complex methods for calculating the dose for a child according to the anesthetic dose in adults, and according to the body surface reported to the weight. Clark and Young's different formulas lead to close results. The ADA and the FDA offer the conversion charts appearing in the two tables 1 and 2.

Although in practice the problem seldom arises, the use of the local anesthetic and the vasoconstrictor for a child of less than 6 months is contra-indicated taking into account the low metabolic capacities which can lead to an overdose or an accumulation of the free fraction.

Table 1: Child dosage according to the weight calculated according to the usual dose for the adult. According to Berini and Gay, 1997.

Weight of the child in kg	Fraction of the adult dose
10	0.27
15	0.36
20	0.48
25	0.55
30	0.62
35	0.69
40	0.75

Table 2: Comparison of the total doses recommended by the Food and Drug Administration in lidocaine 2% with adrenaline and mepivacaine in adults and children. According to Walh, 1997.

	Mepivacaine à 3 %	Lidocaine 2 % + adrenaline
Anesthetic dose per carpule of 1.8 ml	54 mg	36 mg
Maximum number of cartridges in 24 hours for a 70 kg adult	7.4	13.9
Maximum number of cartridges in 24 hours for a 25 kg child	2.8	4,4

7.3. The elderly subject

The elderly subject is often the target of the various disorders which have already been reviewed in this report. It is moreover traditional to consider subjects beyond 70 years as patients with chronic renal insufficiency (after 40 years the glomerular filtration rate lowers 1 ml per minute and per annum) what forces to decrease the total dose by one-third from 70 to 80 years and by half beyond (Commissionnat and Rimet, 1992 [LoP IV]).

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