Inhibition of bacterial growth by different mixtures of propofol and thiopentone

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ABSTRACT

Propofol is, as a result of its formulation, an ideal bacterial and yeast culture medium. An outbreak of sepsis in humans and an increase in wound infections in dogs has been ascribed to the use of propofol. It has been previously reported that a 1:1 mixture of propofol and thiopentone has bactericidal properties. This study was undertaken to determine if further serial mixtures of propofol and thiopentone maintained the bactericidal properties. Mixtures of 1:1 (solution A), 5:1 (solution B), 10:1 (solution C), 50:1 (solution D) and 100:1 (solution E) of 1 % propofol to 2.5 % thiopentone, 2.5 % thiopentone (solution T), 1 % propofol (solution P) and saline (solution S) were prepared and inoculated with between 10^5 and 10^6 colony-forming units of *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans*. A sample was withdrawn from each solution at 0, 1, 6, 12, 48 and 120 hours after inoculation and a bacterial count was performed. This study showed that thiopentone and solution A behaved in similar fashion by inhibiting bacterial growth and was bactericidal after 48 hours. Solution B was not bactericidal against *S. aureus* and *C. albicans*. Propofol and solutions D and E all supported growth of all the organisms tested. These data indicate that mixtures of propofol and thiopentone at a ratio less than 1:1 do not maintain the bactericidal properties.

Key words: bacterial growth, preservation, propofol, thiopentone.

INTRODUCTION

Propofol is a phenol-based anaesthetic agent used for the induction and maintenance of anaesthesia in dogs and cats[2,4,7,10,11,14,16,18,20,22,24–27]. Propofol due to its formulation stimulates the growth of bacteria and yeasts[6]. It is formulated in an isotonic emulsion of glycerol, egg phosphatide, sodium hydroxide and soya bean oil in water[13]. The Centres for Disease Control in the United States have indicated that propofol has played a role in small outbreaks of sepsis in human patients[6]. An increase in wound infections in veterinary medicine has been associated with the use of propofol[12]. Reuse of a propofol vial led to the death of a cat from septicaemia 2 hours after administration. A heavy growth of *Enterobacter*

aerogens was isolated from all the organs of the cat and from the remaining fluid in the propofol vial (Bacteriology results, Department of Veterinary Tropical Diseases, University of Pretoria, 1996). Manufacturers recommend that an aseptic technique be used when handling the drug; the contents should be used immediately after being drawn up into a sterile syringe and the contents of an open ampoule should discarded within 6 hours[6].

Thiopentone is a strongly alkalotic (pH 10) barbiturate anaesthetic agent with bactericidal properties[6]. Thiopentone (2.5 %) and propofol (1 %) were combined in 1:1 mixture for the induction of anaesthesia in humans[21]. The combination of propofol and thiopentone was noted to be synergistic in action, and induction and recovery characteristics were similar to propofol alone and a reduction in costs was evident[21,23]. In the initial studies propofol and thiopentone were administered into separate venous drainage pools as it was unknown if they were chemically compatable[21]. Chemical stability studies demonstrated that propofol and thiopentone combined in 1:1 mixture in

the same polypropylene syringe were chemically stable at room temperature for 5 days and for a week at 4 °C[3,17].

The cardiovascular and respiratory effects of a 1:1 mixture of thiopentone and propofol have been investigated in dogs[15]. This study concluded that the combination induced changes in cardiovascular and respiratory functions similar to either thiopentone alone or propofol alone[15]. The quality and time to recovery were similar for the 1:1 mixture and propofol but the recovery from thiopentone was inferior to the combination or propofol alone[15].

Microbiological growth in the propofol-thiopentone combination has been investigated. It was found that a 1:1 combination of propofol and thiopentone was bactericidal to *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa* in contrast to propofol alone which supported growth[6]. The 1:1 mixture inhibited the growth of *Candida albicans*[6].

It is known that cats and sighthounds have an inability to metabolise thiopentone and that recovery from anaesthesia can be prolonged when thiopentone is used as the sole anaesthetic agent[5,28]. Thiopentone has been shown to have an adverse outcome on puppies if used for caesarean sections[1]. Propofol has been shown to be superior to thiopentone for general anaesthesia in humans undergoing caesarean section[1,8,9,29]. If preservation of propofol by thiopentone could be achieved at a low concentration of thiopentone the mixture could be a more acceptable anaesthetic agent in these patient subgroups. The aim of this study was to determine if lower concentrations of thiopentone would maintain acceptable bactericidal properties.

MATERIALS AND METHODS

Standard bacterial suspensions of approximately 1×10^6 colony-forming units per millilitre (CFU/mℓ) were made using reference cultures of *Staphylococcus aureus* (ATCC 25213), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and a clinical isolate of *Candida albicans*. The bacterial concentration was determined optically as rapidly

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growing cultures were preferred for use in this test. The final concentrations achieved were *S. aureus* 1.79×10^6 CFU/ml, *P. aeruginosa* 4.3×10^5 CFU/ml, *E. coli* 7×10^5 CFU/ml and *C. albicans* 3.5×10^4 CFU/ml.

Sterile aliquots were prepared in a laminar-flow cabinet with saline (0.9 % sodium chloride, Fresenius Kabi, Midrand) (solution S), thiopentone (Thiopentone sodium, Fresenius Kabi) (solution T), propofol (Propofol 1 %, Frasenius Kabi) (solution P) and various mixtures of propofol and thiopentone to a total volume of 10 ml. Propofol (1 %) and thiopentone (2.5 %) were mixed in ratios of 1:1 (solution A), 5:1 (solution B), 10:1 (solution C), 50:1 (solution D) and 100:1 (solution E). The sterile containers were randomly labelled to blind the bacteriologist to the identity of the various mixtures. The bacteriologist was able to identify the thiopentone and saline solutions due to the colour of the liquids. Each mixture and the controls were inoculated with 0.5 ml of the bacterial or yeast strain solution. The solutions were incubated at 25 °C to emulate room temperature. A sample of 0.1 ml was withdrawn from each solution at 0, 1, 6, 12, 48 and 120 hours after inoculation. A standardised plate counting method was performed on each of the solutions to enumerate the viable bacteria and yeasts present. The samples were diluted ten-fold in sterile 0.9 % saline up to a mixture of 10^{-6}. 0.2 % of Polysorbate 80 (Tween® 80, Merck, South Africa) was added to the saline to aid dispersal of the microorganisms. A volume of 0.1 ml was withdrawn from each of these mixtures and spread onto nutrient agar (Oxoid, Basingstoke, UK) plates in the case of the bacteria and potato dextrose agar (Difco Laboratories, Surrey, UK) plates in the case of *C. albicans.* The plates were incubated at 37 °C, in air, for 24 hours and thereafter colony counts were done. The number of colony-forming units (CFU)/ml cultured per bacterial strain was recorded at each time interval for each solution. As 0.1 ml was sampled for the 10 ml aliquot, a CFU count of 0 could have come from a solution containing less than 100 CFU/ml. The solutions were designated as containing $<1.00 \times 10^2$ CFU/ml.

Data were entered into a spreadsheet (Excel, Microsoft Corporation, Redmond) and analysed using a commercial statistical package (SigmaStat 2.0, Jandel Scientific). Statistical significance was set at a $P < 0.05$. A 1-way analysis of variance of ranks was used to test for statistical differences between solutions while a pair-wise multiple comparison using Dunnett's Method was used to identify
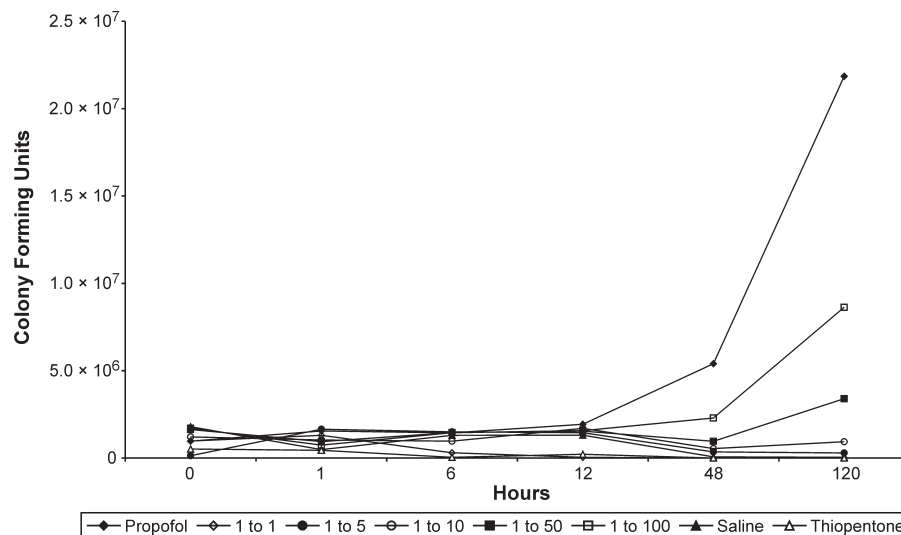

Fig. 1: **Growth of *Staphylococcus aureus* in propofol, thiopentone, saline and mixtures of propofol and thiopentone. Rapid growth in propofol and low mixtures of thiopentone is evident. The *x*-axis represents time in hours while the *y*-axis represents colony-forming units on an exponential scale.**

statistically different groups with thiopentone, propofol and saline serving as control groups. Pearson's product moment correlation was used to determine the correlation over time between groups.

RESULTS

S. aureus grew rapidly in solution S, achieving a count of 2.2×10^7 CFU/ml over the 120 hours. Growth in solutions D and E was also rapid but less than the growth in propofol alone. Solution C maintained the CFU/ml count achieved at baseline throughout the study. Bacterial counts decreased in solution B while solution A had bacterial count after 48 hours. In solution S bacterial counts remained stable for 48 hours after which they tended to decrease. Solution T was statistically different from all other groups ($P < 0.05$). Solution P was statistically different from solutions T, A, B, C and S. A positive correlation was found between solutions P and E (0.990, $P < 0.0002$) and D (0.887, $P < 0.019$). Solutions D and E were positively correlated (0.936, $P < 0.006$). Solution T was positively correlated to solution A (0.873, $P < 0.023$). The growth of microorganisms is graphically depicted in Fig. 1 and the actual values are given in Table 1.

P. aeruginosa grew rapidly in solutions P, C, D and E. Initially some growth of *P. aeruginosa* was seen in solution T. No colonies were cultured after 48 hours in solutions T and A and after 120 hours in solution B. Bacterial counts in solution S remained constant. Solution T was statistically different to solutions P, C, D, E and S ($P < 0.05$). Solution P was statistically different to solutions T, A and B ($P < 0.05$). A positive correlation was found between

solutions P and E (0.999, $P < 0.001$), D (0.991, $P < 0.001$) and C (0.863, $P < 0.027$). A negative correlation was found between solutions P and T (–0.913, $P < 0.011$) and A (–0.0874, $P < 0.023$). A positive correlation was evident between solutions T and A (0.942, $P < 0.005$). A negative correlation was present between solutions A and D (–0.878, $P < 0.021$) and E (–0.869, $P < 0.024$). A negative correlation was present between solutions B and C (–0.881, $P < 0.020$). A positive correlation was present between solutions E and C (0.876, $P < 0.022$) and D (0.987, $P < 0.001$). A negative correlation was present between solutions T and D (–0.924, $P < 0.008$) and E (–0.916, $P < 0.011$). The growth of microorganisms is graphically depicted in Fig. 2 and the actual values are given in Table 1.

E. coli followed a similar trend to *P. aeruginosa* with rapid bacterial growth occurring in solutions P, D and E. Solution C showed a decrease in bacterial count up to 12 hours before the counts increased again. No bacteria were cultured from solutions T, A and B after 48 hours. Bacterial counts in solution S remained stable throughout the study. Solution T was statistically different to solutions D, E and P ($P < 0.05$). Solution P was positively correlated to solutions C (0.987, $P < 0.001$), D (0.999, $P < 0.001$) and E (0.998, $P < 0.001$). Solution T was positively correlated to solution A (0.885, $P < 0.019$). A positive correlation was present between solutions C and D (0.989, $P < 0.001$), E (0.992, $P < 0.001$) and S (0.903, $P < 0.014$). Solution D was positively correlated to solution E (0.996, $P < 0.001$). The growth of microorganisms is graphically depicted in Fig. 3 and the actual values are given in Table 1.

Table 1: **Colony-forming units cultured. The counts are given as CFU/ml. A count of <1.00 × 10^2 indicates that no bacteria or yeasts were cultured.**

Time	Solution P*	Solution A	Solution B	Solution C	Solution D	Solution E	Solution S	Solution T
Staphylococcus aureus								
0	9.66×10^5	9.74×10^5	1.37×10^5	1.21×10^6	1.63×10^6	1.70×10^6	1.79×10^6	5.18×10^5
1	1.55×10^6	1.30×10^6	1.65×10^6	1.03×10^6	9.40×10^5	7.40×10^5	4.80×10^5	4.40×10^5
6	1.44×10^6	3.03×10^5	1.50×10^6	9.70×10^5	1.46×10^6	1.45×10^6	1.30×10^6	3.80×10^4
12	1.93×10^6	4.56×10^4	1.45×10^6	1.70×10^6	1.54×10^6	1.57×10^6	1.31×10^6	2.20×10^5
48	5.40×10^6	$<1.00 \times 10^2$	3.50×10^5	5.45×10^5	9.55×10^5	2.30×10^6	6.25×10^4	$<1.00 \times 10^2$
120	2.19×10^7	$<1.00 \times 10^2$	2.90×10^5	9.30×10^5	3.40×10^6	8.63×10^6	3.80×10^4	$<1.00 \times 10^2$
Pseudomonas aeruginosa								
0	1.09×10^5	2.90×10^5	2.83×10^5	3.33×10^5	4.27×10^5	1.92×10^6	4.32×10^5	2.00×10^5
1	6.50×10^5	5.40×10^5	3.07×10^5	2.94×10^5	4.02×10^5	4.76×10^5	8.70×10^5	4.00×10^5
6	7.20×10^5	2.50×10^5	2.50×10^5	3.31×10^5	4.34×10^5	4.75×10^5	8.90×10^5	3.00×10^5
12	5.67×10^5	4.50×10^5	2.29×10^5	3.86×10^5	1.50×10^6	3.39×10^6	1.21×10^6	2.80×10^5
48	5.53×10^7	$<1.00 \times 10^2$	3.30×10^5	6.20×10^6	2.97×10^7	6.65×10^7	3.56×10^5	$<1.00 \times 10^2$
120	6.86×10^7	$<1.00 \times 10^2$	$<1.00 \times 10^2$	2.66×10^7	2.96×10^7	8.60×10^7	5.43×10^5	$<1.00 \times 10^2$
Escherichia coli								
0	4.31×10^4	4.10×10^5	5.49×10^4	3.70×10^5	6.20×10^5	5.20×10^5	7.03×10^5	4.70×10^5
1	3.74×10^5	5.50×10^5	4.50×10^5	3.23×10^6	2.94×10^6	4.09×10^5	6.00×10^5	4.30×10^5
6	3.74×10^5	3.80×10^5	4.30×10^5	4.45×10^4	3.86×10^5	3.70×10^5	5.50×10^5	3.90×10^5
12	4.33×10^6	2.70×10^5	2.60×10^5	4.63×10^4	1.77×10^6	4.03×10^6	3.16×10^5	3.40×10^4
48	2.81×10^7	$<1.00 \times 10^2$	$<1.00 \times 10^2$	9.70×10^6	2.94×10^7	1.85×10^7	3.65×10^5	$<1.00 \times 10^2$
120	8.00×10^7	$<1.00 \times 10^2$	$<1.00 \times 10^2$	4.07×10^7	8.02×10^7	6.24×10^7	1.66×10^6	$<1.00 \times 10^2$
Candida albicans								
0	1.57×10^5	2.10×10^5	9.25×10^4	2.50×10^5	1.30×10^5	2.88×10^5	1.01×10^5	2.60×10^5
1	6.00×10^5	5.20×10^5	3.40×10^5	4.20×10^5	5.70×10^5	2.80×10^5	3.65×10^5	5.40×10^5
6	1.90×10^5	2.80×10^5	3.30×10^5	3.70×10^5	3.70×10^5	3.30×10^5	2.11×10^5	4.30×10^5
12	2.70×10^5	3.10×10^5	3.40×10^5	4.50×10^5	2.80×10^5	4.60×10^5	2.12×10^5	3.80×10^5
48	2.82×10^5	2.80×10^3	3.65×10^3	3.97×10^5	2.65×10^5	2.50×10^5	1.01×10^5	5.00×10^1
120	7.70×10^5	$<1.00 \times 10^2$	5.93×10^4	7.70×10^4	5.02×10^5	9.20×10^5	1.10×10^5	$<1.00 \times 10^2$

*Mixtures of 1:1 (Solution A), 5:1 (Solution B), 10:1 (Solution C), 50:1 (Solution D) and 100:1 (Solution E) of 1% propofol to 2.5% thiopentone, 2.5% thiopentone (Solution T), 1% propofol (Solution P) and saline (Solution S).

C. albicans growth was slow and exponential growth was not evident as for the other 3 organisms in solution P. A continual increase in *C. albicans* was evident in solutions P, D and E. Yeast counts decreased in solutions B and C while none were viable after 120 hours in solutions T and A. Yeast counts in solution S remained stable. No statistical difference was present between any of the groups. A positive correlation was found between solutions A and B (0.870, *P* <0.024), S (0.910, *P* <0.012) and T (0.972, *P* < 0.002). Solutions T and B were positively correlated (0.924, *P* <0.008). The growth of microorganisms is graphically depicted in Fig. 4 and the actual values are given in Table 1.

DISCUSSION

Bacterial growth in propofol has been responsible for the outbreak of infections in humans and dogs[6,12]. Various methods have been sought to preserve propofol, including the addition of calcium EDTA and metabisulphite[19]. Thiopentone is freely available in most veterinary practices and most practitioners would be able to combine propofol and thiopentone to prevent bacterial growth. This study enabled us to better understand the use of thiopentone to prevent bacterial and yeast growth in propofol.
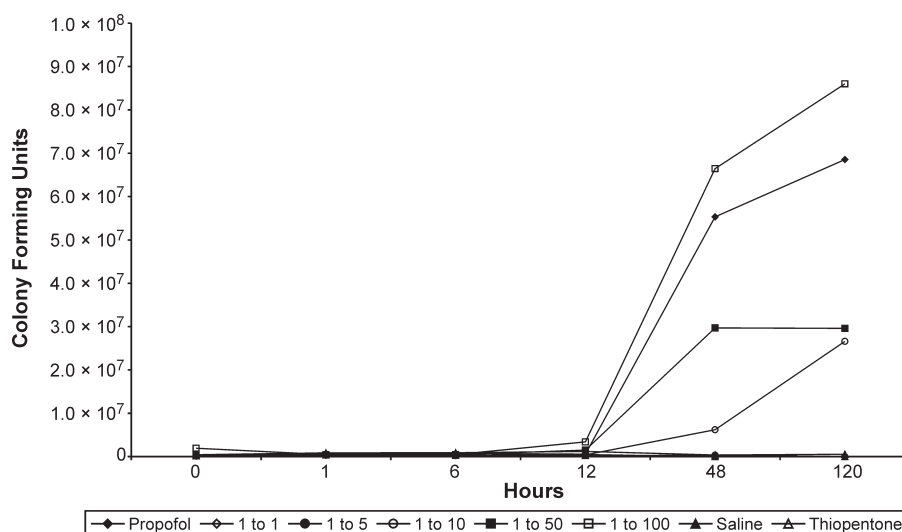

Fig. 2: **Growth of *Pseudomonas aeruginosa* in propofol, thiopentone, saline and mixtures of propofol and thiopentone. Rapid growth in propofol and low mixtures of thiopentone is evident. The *x*-axis represents time in hours while the *y*-axis represents colony-forming units on an exponential scale.**

S. aureus, E. coli and *P. aeruginosa* grew rapidly in solutions P, D and E. The rapid growth in propofol only is in agreement with published results in the literature[6]. The initial study by Crowther *et al.* examined only 1 mixture of propofol and thiopentone (1:1)[6]. Our study examined further mixtures down to a ratio of 100:1. From these results it is evident that further mixtures to a ratio less than 1:1

does not maintain the bactericidal properties of thiopentone for all tested bacteria. Solution B does have an inhibitory effect on bacterial growth for all bacteria tested.

There are some general agreements between our study and that of Crowther *et al.*[6]. A dramatic decrease in CFU of *S. aureus* was seen over 24 hours[6]. In our study the thiopentone only became
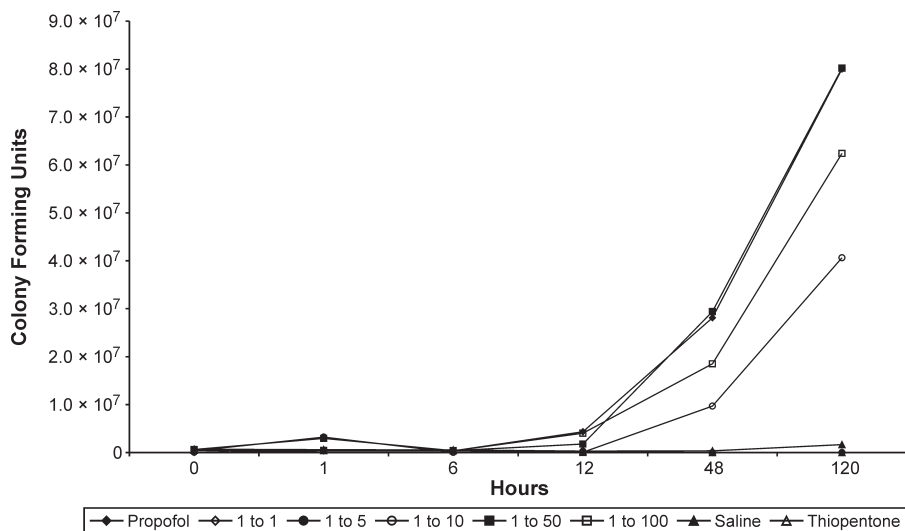
Fig. 3: **Growth of *Escherichia coli* in propofol, thiopentone, saline and mixtures of propofol and thiopentone. Rapid growth in propofol and low mixtures of thiopentone is evident. The *x*-axis represents time in hours while the *y*-axis represents colony-forming units on an exponential scale.**
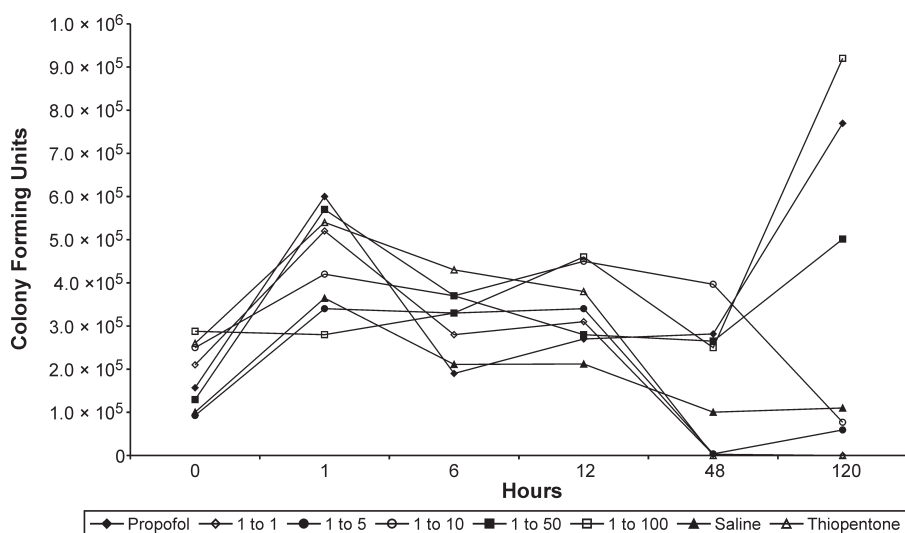

Fig. 4: **Erratic growth of *Candida albicans* in propofol, thiopentone, saline and mixtures of propofol and thiopentone. The *x*-axis represents time in hours while the *y*-axis represents colony-forming units on an exponential scale.**

bactericidal for *S. aureus* at 48 hours. *E. coli* and *P. aeruginosa* were killed by thiopentone at 3 hours[6] where as in our study this occurred after only 12 hours.

Crowther *et al.* suggested that propofol was not a universal growth medium and specifically used the growth of *P. aeruginosa* to support this concept[6]. Our study showed a poor growth of *P. aeruginosa* up to 12 hours but by 48 hours counts had reached above 5×10^6 and continued to grow rapidly.

Crowther suggested that cooler temperatures of incubation may slow the growth of *S. aureus*[6]. Our study and that of Crowther[6] were performed at similar temperatures. *Pseudomonas* spp. are environmental bacteria and are usually not as affected by temperature as *S. aureus*. This supports the concept that propofol is not a universal growth medium.

In Crowther's study, *C. albicans* was not eliminated from the 1:1 mixture after 24 hours of incubation[6]. Our data support and further indicate that the fungicidal properties only became evident after 48 hours of incubation. During this 48-hour period *C. albicans* CFU/mℓ remained constant, indicating that thiopentone and 1:1 mixture with propofol is static and only becomes bactericidal after this time period.

Crowther suggested that the bactericidal properties of thiopentone may be related to pH[6]. On serial dilution during the counting procedure, CFU counts increased, indicating the removal of the bacteriostatic agent. This was particularly evident for the cultures with *C. albicans* and *S. aureus*. Dilution with saline would have decreased the pH and hence if pH

drove the static effect, bacterial growth would again continue.

This study used the same isolates of *E. coli* and *P. aeruginosa* that were used in Crothwer's study[6] but a different reference isolate of *S. aureus* and a clinical isolate of *C. albicans* were used. The reference strain of *S. aureus* and the clinical isolate of *C. albicans* behaved similarly to other published reports and should not have affected the results.

This study showed that thiopentone and a 1:1 mixture of propofol and thiopentone behaved in similar fashion by inhibiting bacterial growth and being bactericidal after 48 hours. The 5:1 mixture was not bactericidal with *S. aureus* and *C. albicans*. Propofol, and 100:1 and 50:1 combinations, behaved in a similar fashion and all supported bacterial growth. These data indicate that further mixture of propofol with thiopentone to below 1:1 does not maintain the bactericidal properties.

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