Central Nervous System toxicity of mefenamic acid overdose compared to other NSAIDs: an analysis of cases reported to the United Kingdom National Poisons Information Service.

Running header: CNS toxicity of mefenamic acid

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Keywords: Mefenamic acid, non-steroidal anti-inflammatory drug, overdose, poisoning, CNS toxicity, convulsions.

Word count: 2,734**;** **Tables** 5; **Figures** 1; **Supplementary Figures** 1.

What is already known about this subject:

Central nervous system toxicity has been reported following severe non-steroidal anti-inflammatory drug (NSAIDs) overdose. Small case series and case reports have suggested overdose with mefenamic acid is commonly followed by Central Nervous System (CNS) toxicity, especially convulsions.

What this study adds:

The study demonstrates that mefenamic acid overdose carries a significantly higher risk of dose-related CNS toxicity compared with other commonly used NSAIDs and the risk of convulsion is substantially higher.

Summary

Aims: Case reports and small case series suggest increased Central Nervous System (CNS) toxicity especially convulsions, after overdose of mefenamic acid, compared with other NSAIDs, but comparative epidemiological studies have not been conducted. This study compared rates of CNS toxicity after overdose between mefenamic acid, ibuprofen, diclofenac and naproxen, as reported in telephone enquiries to the United Kingdom National Poisons Information Service (NPIS).

Methods: NPIS telephone enquiries related to the four NSAIDs received between January 2007 and December 2013 were analysed, comparing the frequency of

reported CNS toxicity (convulsions, altered conscious level, agitation or aggression, confusion or disorientation) using multivariable logistic regression.

Results: Of 22,937 patient-specific telephone enquiries, 10,398 did not involve co-ingestion of other substances (mefenamic acid 461, ibuprofen 8090, diclofenac 1300, naproxen 547). Patients taking mefenamic acid were younger and more commonly female than those using other NSAIDs**.** Those ingesting mefenamic acid were more likely to experience CNS toxicity than those ingesting the other NSAIDs combined (adjusted OR 7.77, 95% CI 5.68 to 10.62), especially convulsions (adjusted OR 81.5, 95% CI 27.8 to 238.8). Predictors of CNS toxicity included reported dose and age, but not gender.

Conclusions: Mefenamic acid overdose is associated with a much larger and dose-related risk of central nervous system toxicity, especially convulsions, compared with overdose of other NSAIDs. The benefit–risk profile of mefenamic acid should now be re-evaluated in light of effective and less toxic alternatives.

(233 words)

Tables of Links

TARGETS	
Other protein targets[a]	**Enzymes**[e]
FABP4	Acetyl CoA carboxylase
TNF-α	Adenylate cyclase
GPCRs[b]	Akt (PKB)
GLP-1 receptor	ERK1
Nuclear hormone	ERK2

receptors[c]	
PPARγ	FASN
Transporters[d]	Hormone sensitive lipase (HSL)
GLUT4	**PKA**

LIGANDS	
Adiponectin	IBMX
cAMP	IL-6
Dexamethasone	Indomethacin
Exenatide (exendin-4)	Insulin
Exendin (9-39)	Liraglutide
GLP-1	**Metformin**

These Tables of Links list key protein targets and ligands in this article that are hyperlinked* to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander et al., 2015a,b,c,d,e).

Introduction

Mefenamic acid is a fenamate non-steroidal anti-inflammatory drug (NSAID) licensed since the early 1960s as a prescription only medicine in the UK and Europe (1) and often used for the treatment of dysmenorrhoea and heavy menstrual bleeding (HMB). Although this use was supported by clinical trials [2-4]; and by recommendations in published guidelines (5,6), more recent evidence has not suggested clinically important benefits for mefenamic acid compared with other NSAIDs for either indication (7-9). While NSAIDs are cited as treatment options in current guidance, mefenamic acid is not specifically recommended for treating dysmenorrhoea (10) or HMB (11).

The propensity of mefenamic acid overdose to induce Central Nervous System (CNS) toxicity, particularly convulsions, has been reported in a number of case reports and small

case series (12-19), but the differential neurotoxicity of individual NSAIDs, in overdose and normal use, and the influence of other risk factors on the development of neurotoxicity have not previously been reported.

It is now acknowledged that, when considering the risks and benefits of medicines, the risks produced by overdose should be taken into account, as well as those associated with normal therapeutic use. In the European Union, Directive 2010/84/EU now requires that member states operate a pharmacovigilance system that collects information on suspected adverse reactions from use of medicines outside of (as well as within) the terms of their marketing authorisation, including those occurring after overdose (20). One potentially valuable way of doing this is by using data collected by poisons centres when they provide advice on cases of suspected poisoning.

This study was therefore performed to compare the frequency of neurological toxicity between mefenamic acid and other commonly used NSAIDs following overdose using data collected routinely by poisons centres in the UK, and to examine the effects on this of age, gender and reported ingested dose.

Methods

The National Poisons Information Service (NPIS) is commissioned by Public Health England to provide information and clinical advice for registered health care professionals throughout the UK on all aspects of acute and chronic poisoning. For this study, information was extracted from the clinical records of telephone enquiries to the NPIS, after full anonymisation. These data included patient age and sex, reported dose and route of exposure, concomitant medication exposures and clinical features reported during the telephone enquiry. Circumstances of exposure were classified by the information scientist

taking the enquiry (e.g. intentional overdose, accidental overdose including therapeutic errors, drug misuse). Where it could be established that more than one enquiry had been made about the same patient and exposure, the clinical information was consolidated into a single record. CNS toxicity was defined as any of the following: convulsions, altered conscious level, agitation, aggression, confusion or disorientation.

To standardise for doses between drugs, we calculated the ratio of reported ingested dose to the maximum daily dose, expressed in this study as ingested-to-maximum dose ratio. When available, the maximum recommended daily dose used was that advised by the British National Formulary (BNF) (21) (Table 1). Mefenamic acid is not licensed for children less than 12 years of age so there is no recommended daily dose for this group. We therefore used a maximum daily dose in mg/kg derived from the maximum adult dose and assuming an adult weight of 70 kg.

For children, when the maximum daily dose was expressed in mg/kg in the BNF, and when the child's weight was not documented, the weight was assumed using the age and the 50th percentile of the male or female growth charts produced by the World Health Organisation and the Royal College of Paediatrics and Child Health (22).

A sensitivity analysis was conducted to assess the robustness of the results using an alternative approach that employed the toxic threshold doses for each NSAID as listed on TOXBASE®, the online poisons information database provided for UK health professionals by the NPIS (Table 1). When available, reported drug doses were standardised by recorded weight; when this was not documented the weight of adults was assumed to be the average weight for a male (84 kg) or female (70 kg) from the National Statistics Health Survey for England 2012 and the Welsh Health Survey 2009 (23, 24). For children, the weight was calculated as described above. For a 70 kg adult these toxic threshold doses are 1.9 (mefenamic acid) to 3.3 (diclofenac) times the maximum daily dose as recommended in the

British National Formulary. We then standardised for doses between drugs by calculating the ratio of reported ingested dose to the toxic dose, expressed in this study as ingested-to-toxic dose ratio (Table 1).

When analysing the clinical manifestations of toxicity, patients reported to be exposed to other drugs were excluded. Logistic regression models were applied using IBM SPSS v.22 software to compare the odds of developing CNS toxicity between different NSAIDs. Likelihood ratio tests were used to compare models with drug type included as a covariate to one in which it is excluded to determine whether drug type was a significant predictor of outcome. Where significant differences were observed, pairwise comparisons were made between each of the pairs of drugs and the p-values were adjusted using the Bonferroni correction for multiple testing. This model could not be applied to the analysis of reported cases of convulsions as the number of patients who developed convulsions was small and not all NSAIDs were associated with a case of convulsion. Instead, additional models were constructed for the CNS toxicity outcome and for convulsions in which mefenamic acid was compared to all other NSAIDs.

Multivariable logistic regression models were used to test for differences between drugs after adjusting for age, gender and ingested-to-toxic dose ratio. To allow for a possible quadratic relationship between age and odds of toxicity, age-squared was added as a term in the models. Terms allowing for interactions between drug, age, sex and ingested dose were also tested for, but were not statistically significant and so not included in the final models. Patients with no data on age, sex or ingested doses available were excluded in this model.

Ethical approval is not required in the UK for surveillance studies of this type because they involve analysis of anonymised aggregated clinical information that is collected routinely as part of the NPIS clinical record.

Results

Between January 2007 and December 2013 there were 23,144 NPIS telephone enquiries relating to 22,937 separate exposures to the four NSAIDs studied. Exposures were less common for mefenamic acid (925) than for ibuprofen (17,302), diclofenac (3,385) or naproxen (1,325). The median age of mefenamic acid patients was younger (17 years) than those involved in enquiries about ibuprofen (23 years), diclofenac (29 years) or naproxen (32 years) and there was a significantly higher proportion of female patients in the mefenamic acid group compared to the other groups combined (P <0.0001, Table 2). A higher proportion of mefenamic acid exposures involved intentional overdose and a lower proportion accidental overdose, including therapeutic errors, compared to the other NSAIDs studied. Acute intentional overdose was the most prevalent exposure type overall (Table 2).

There were 10,398 exposures to one of the studied NSAIDs where co-exposure to other drugs was not reported. In these, CNS toxicity was recorded in 3% overall (Table 3) and, after adjustment for age, sex and reported dose ingested (ingested-to-maximum daily dose ratio), was significantly more common with mefenamic acid than with ibuprofen (adjusted Odds Ratio [aOR] 11.96), diclofenac (aOR 8.) or naproxen (aOR 3.83) (Table 4) and with the 3 comparator NSAIDs combined (aOR 7.77). CNS toxicity was also reported significantly more often after overdose with naproxen compared with ibuprofen (aOR 3.12) and diclofenac (aOR 2.37).

Convulsions were reported in 42 (9.1%) mefenamic acid enquiries, compared to 5 (0.1%) with ibuprofen, 1 (0.1%) with diclofenac and none involving naproxen. The risk of convulsions was significantly higher after mefenamic acid than the other three NSAIDs combined (aOR 81.5, Table 4).

Following mefenamic acid overdose, reported dose was a significant predictor of both CNS toxicity and convulsions, both before and after adjustment for age and sex (P <0.001) (Table

5). Similarly, age was associated significantly with CNS toxicity in both models, but was not a significant predictor of convulsion after adjustment. The relationship between age and CNS toxicity was quadratic, with the risk initially increasing with age before reaching a peak and decreasing (Figure 1 and Supplementary Figure). For CNS toxicity the odds were highest at age 21 years in unadjusted analysis and 22 years in the adjusted analysis. For convulsions, the odds were highest at the ages of 18 years and 17 years in the unadjusted and adjusted analyses, respectively. Sex was not significantly correlated with CNS toxicity or convulsions.

In sensitivity analyses, the alternative method of dose adjustment, using ingested-to-toxic dose ratio as defined by TOXBASE®, produced results consistent with the original analyses (data not shown). Estimated odds ratios for differences in risk between drugs were almost identical in magnitude, with no changes in terms of statistical significance or interpretation. As in the original analysis, the ingested-to-toxic dose ratio was a significant predictor of both CNS toxicity and convulsions, and sex was not related to any of the outcomes. However, age was significantly associated with CNS toxicity in general, but not with convulsions.

Discussion

This study confirms that mefenamic acid overdose is commonly associated with dose-related CNS toxicity, especially convulsions, and that this is substantially more common than after overdose with other commonly used NSAIDs. Although intentional overdose formed a larger proportion of mefenamic acid enquiries, the average reported dose taken (as a proportion of the maximum recommended dose) was almost identical for each NSAID studied and the difference persisted after adjustment for ingested doses.

These results are consistent with previous research in animals and humans. In mice, single large doses of mefenamic acid caused CNS stimulation, followed by incoordination, CNS

depression and convulsions (25). Clinical features of CNS toxicity reported in humans range from mild drowsiness and disorientation to convulsions, coma and respiratory arrest (12-16, 26, 27). Convulsions usually occur 2-7 hours after overdose but can occur up to 12 hours after ingestion (13, 28). A retrospective review carried out by the Swiss Toxicological Information Centre examined the rates of acute overdose by a single drug between 1997 and 2010 that had resulted in at least one convulsion. Mefenamic acid overdose accounted for 16.3% of all cases. Overall, 11% of mefenamic acid patients developed convulsions, which occurred more frequently in 15 to 19-year-olds (23.9%) than in those 20 years and older (6.0%, $p < 0.001$) (27).

There is some evidence that the risk of developing convulsions is dose or plasma concentration related (13, 29, 30). In a prospective study of 54 patients with mefenamic acid overdose, mean plasma mefenamic acid concentrations at admission were significantly higher in patients presenting with convulsions than those without. Most patients developing seizures had plasma mefenamic acid concentrations above a line joining 100 mg/L at two hours with 5 mg/L at 15 hours, which is substantially higher than those seen during therapeutic dosing (1-10 mg/L) (13). However, seizures can occur in patients with mefenamic acid concentrations below this threshold line (13, 15, 16) and the lowest 4-hour mefenamic acid concentration at which convulsion has been documented was 21 mg/L in a 13-year-old girl (15).

In the retrospective Swiss study described above, the reported dose ingested was related directly to the severity of the toxicity, including CNS toxicity, and the lowest dose at which moderate or severe symptoms developed was 3.5 grams (27). The smallest mefenamic acid overdose reported to cause convulsions was 2.5 grams (28). Furthermore, mefenamic acid has also been linked to seizures following therapeutic doses (14, 31). While these earlier studies provide evidence of a dose-related risk of convulsion after mefenamic acid overdose, they do not compare risk with alternative NSAIDs.

The exact mechanism by which NSAIDs induce seizures in overdose is not clear. It has been postulated that NSAIDs reduce the convulsive threshold by inhibiting cerebral prostaglandin and/or thromboxane synthesis (32). Modulation of GABA receptors in the CNS has also been suggested as a possible cause for lowering seizure threshold in poisoned patients (33-35). The propensity of mefenamic acid to be more neurotoxic in overdose than other NSAIDs is currently unexplained; information is lacking on the relative potency of individual NSAIDs for reducing convulsive threshold and no comparative data are available regarding the efficiency of different NSAIDS in penetrating the blood brain barrier.

The findings of this study are important because of the physical risk from convulsions, including risk of injury, aspiration and hypoxia. Sudden death may occur, although is probably rare in this context. Social impacts that convulsions may have on the individual are also important, but will vary between countries. For example, the affected patient may not be able to drive for a period of time and employment may be affected for some occupations,

There are important limitations in this study that need to be considered. The number of enquiries made to the NPIS regarding a particular drug or agent, and reported in this study, is not the same as the actual number of patients exposed. The NPIS might also be contacted more than once about the same patient, especially those with severe or prolonged clinical features. Identification and consolidation of duplicate enquiries was attempted but was not always possible and some duplicates might have been missed. Not all cases of overdose are referred to NPIS because the responsible clinician may be confident of management, with or without reference to TOXBASE®. NPIS enquiry numbers are unlikely to correlate directly with patient presentations to hospitals, because advice is less likely to be sought for patients with no or mild clinical features. Details of exposure are as initially reported by the patient and then passed on by the enquirer and this may sometimes be unreliable. Analytical confirmation of exposure and exclusion of other potential toxins is not available as this is not performed as part of the routine care of patients with NSAID

overdose. Although the NPIS attempts to follow up episodes of severe poisoning, this is often not possible, so clinical effects occurring after the enquiry may not be captured, including late onset convulsions, for example. NPIS data does not always identify important confounding factors such as past history of epilepsy, alcohol abuse, or head injury. These limitations, however, apply to all the NSAIDs studied and it is unlikely that systematic bias in data capture between NSAIDs would occur.

Another limitation is created by the difficulty in comparing doses between drugs. Reported doses in the context of drug overdose may be unreliable. Also, mefenamic acid is not licensed for children; hence, no recommended daily dose is available for this population group. A further difficulty is that the weight of the patient is not always documented and had to be inferred in many cases. These limitations, however, are very unlikely to explain the substantial differences between mefenamic acid and other NSAIDs in terms of toxicity and would not have an effect on studying dose-relationship for a specific NSAID. The sensitivity analysis we conducted, standardising doses between drugs using the toxic dose thresholds provided on TOXBASE®, also gave similar results.

In spite of inherent limitations, this study demonstrates the potential value of data collected routinely by poisons centres for assessing the safety of medicines when taken in overdose. It confirms that the risk of CNS toxicity, especially convulsions, is increased after overdose with mefenamic acid compared with other commonly used NSAIDs.

In view of these findings, the balance between benefit and harm for mefenamic acid should now be re-evaluated. Although previously considered an appropriate therapy for menstrual pain and bleeding, (5,6) more recent evidence does not show that mefenamic acid is more effective than other NSAIDs or that NSAIDs are more effective than alternative interventions (7-11). Targeting the drug at women with dysmenorrhoea or menorrhagia is of concern because the teenagers and younger adults commonly affected may also be at increased risk of self-harm (36). As mefenamic acid provides no proven clinical advantages, alternate

drugs should be prescribed to manage inflammatory conditions and menstrual problems, especially in those at higher risk of self-harm. Mefenamic acid should only be considered if alternatives are contraindicated or not tolerated, if used at all. Regulatory authorities should reassess the benefit–risk profile of mefenamic acid, taking into account available information on CNS toxicity with normal use as well as overdose, and consider if further measures are needed to reduce the public health risk from mefenamic acid toxicity.

Competing Interests

The authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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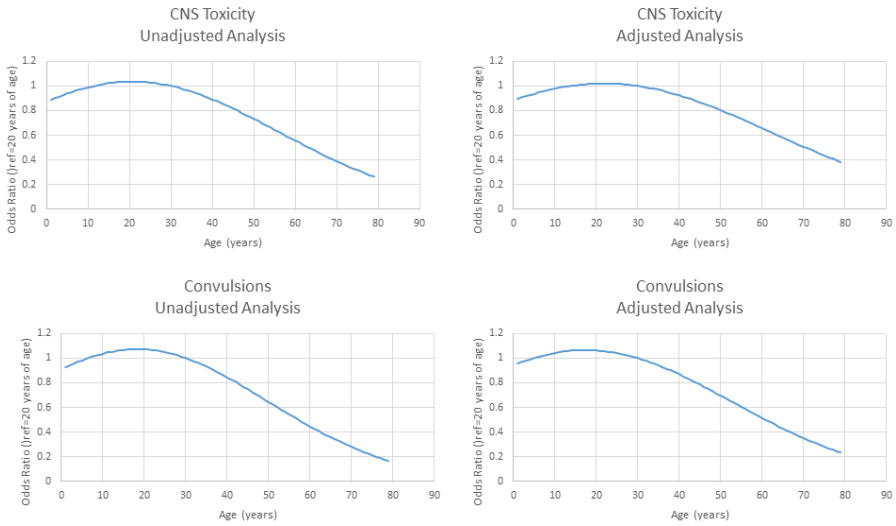

Figure 1: Relationship between age and odds of CNS toxicity and Convulsions. Lines represent the odds at any given age relative to a patient aged 20 years.

Table 1: British National Formulary recommended maximum daily doses for mefenamic acid, ibuprofen, diclofenac, and naproxen, and the toxic doses for each drug as defined on TOXBASE®. Note: The maximum daily dose for any given indication for a drug was used.

	Maximum daily dose		**Toxic dose (mg/kg)**
	Adults (mg)	Children	
Mefenamic acid	1500	• less than 12 years: not licenced • 12-18 years: 1500 mg	40
Ibuprofen	2400	• 1–3 months: 20mg/kg • 3 months-12 years: 30 mg/kg • 12–18 years: 2400 mg	100
Diclofenac	150	• 6 months–18 years: 5mg/kg	7
Naproxen	1250	• 1 month–2 years: 15mg/kg • 2–18 years 10mg/kg	35

Table 2: Patient demographics and exposure types in cases of mefenamic acid, ibuprofen, diclofenac and naproxen overdose reported in enquiries to the NPIS.

		Mefenamic acid		Ibuprofen		Diclofenac		Naproxen	
		n	%	n	%	n	%	n	%
Total		925		17302		3385		1325	
Median (IQR; min-max) Age, (years)		17(14-25; 0-83)		23(2-29; 0-98)		29 (3-40; 0-94)		32(20-45: 0-94)	
Gender	Female	791	85.5%	9817	56.8%	1844	54.5%	693	52.3%
	Male	128	13.8%	7324	42.3%	1513	44.7%	626	47.2%
	Unknown	6	0.7%	161	0.9%	28	0.8%	6	0.5%
Co-administration		464	50.20%	9212	53.2%	2085	61.6%	778	58.7%
Circumstances	Intentional	635	68.6%	7955	46.0%	1790	52.9%	724	54.6%
	Accidental, e.g. therapeutic errors	244	26.4%	8888	51.4%	1486	43.9%	548	41.4%
	Drug misuse	1	0.1%	56	0.3%	6	0.2%	2	0.2%
	Other/Unknown	45	4.9%	403	2.3%	103	3.0%	51	3.8%
Exposure type	Acute (<1 h)	643	69.5%	11602	67.1%	2238	66.1%	761	57.4%
	Staggered (1-24h)	89	9.6%	3361	19.4%	447	13.2%	208	15.7%
	Sub-acute (1 day to 1 month)	22	2.4%	1142	6.6%	204	6.0%	97	7.3%
	Chronic (>1 month)	1	0.1%	142	0.8%	27	0.8%	22	1.7%
	Acute on Chronic	5	0.5%	11	0.1%	8	0.2%	4	0.3%
	Acute on therapeutic	146	15.8%	844	4.9%	399	11.8%	191	14.4%
	Other/Unknown	19	2.1%	200	1.1%	62	1.9%	42	3.2%

Table 3: CNS toxic effects described by health professionals to NPIS after reported overdose of mefenamic acid, ibuprofen, diclofenac, and 2 naproxen. Patients with reported co-exposures have been excluded. Note that some patients may experience more than one feature.

	Diclofenac (n=1300)		**Ibuprofen** (n=8090)		**Mefenamic Acid** (n=461)		**Naproxen** (n=547)	
CNS Toxicity	35	2.7%	163	2.0%	91	19.7%	33	6.0%
Confusion	1	0.1%	12	0.1%	4	0.9%	2	0.4%
Anxiety	1	0.1%	4	0.05%	3	0.7%	1	0.2%
Convulsions	1	0.1%	5	0.06%	42	9.1%	0	0.0%
Reduced conscious level	18	1.4%	92	1.1%	30	6.5%	23	4.2%
Dizziness	15	1.2%	47	0.6%	12	2.6%	5	0.9%
Agitation/Aggression	2	0.2%	7	0.09%	16	3.5%	3	0.5%

Table 4: Adjusted and unadjusted odds ratios for the association between CNS toxicity and drug exposure. Note: to analyse the association between drug exposure and convulsion, a different model was used in which mefenamic acid was compared to all other NSAIDs as the number of patients who developed convulsions was small and not all NSAIDs were associated with convulsion.

	Unadjusted analysis (n= 10,398)				**Adjusted analysis*** (n= 7,711)			
	OR	Lower 95% CI	Upper 95% CI	p-value**		Lower 95% CI	Upper 95% CI	p-value**
CNS Toxicity outcome								
Mefenamic acid v Ibuprofen	11.96	9.07	15.78	<0.001	11.86	8.75	16.07	<0.001
Mefenamic acid v Diclofenac	8.89	5.92	13.35	<0.001	9.02	5.73	14.20	<0.001
Mefenamic acid v Naproxen	3.83	2.52	4.54	<0.001	3.80	2.40	4.49	<0.001
Naproxen v Ibuprofen	3.12	2.13	4.59	<0.001	3.12	2.03	4.79	<0.001
Naproxen v Diclofenac	2.32	1.43	3.77	0.007	2.37	1.37	4.09	0.002
Diclofenac v Ibuprofen	1.35	0.93	1.95	0.116	1.32	0.86	2.01	0.204
Mefenamic acid v all others	9.79	7.52	12.74	<0.001	7.77	5.68	10.62	<0.001
Convulsions outcome								
Mefenamic acid v all others	90.0	34.7	233.2	<0.001	81.5	27.8	238.8	<0.001

Table 5: Adjusted and unadjusted odds ratio for the association between CNS toxicity, convulsions and other independent variables in mefenamic acid overdose patients. Patients with no data available on age, gender or ingested doses were excluded. Note: CNS toxicity odds were highest at age 21 years in unadjusted analysis and 22 years in the adjusted analysis. Convulsions odds were highest at age 18 years in unadjusted and 17 years in adjusted analyses.

	Unadjusted analysis (n=461)				**Adjusted analysis** (n= 405)			
	OR	Lower 95% CI	Upper 95% CI	p-value	OR	Lower 95% CI	Upper 95% CI	p-value
CNS Toxicity								
Age (years)	1.02	1.01	1.03	<0.001	1.14	1.01	1.02	0.014
Age sq (years)	0.999	0.999	1.000	<0.001	0.999	0.999	1.000	<0.001
Sex - Male	(reference)				(reference)			
Female	2.34	0.97	5.63	0.058	1.43	0.52	3.96	0.492
Ingested-to-max dose	1.10	1.06	1.14	<0.001	1.09	1.06	1.13	<0.001
Convulsions								
Age (years)	1.02	1.00	1.03	0.012	1.01	0.996	1.03	0.119
Age sq (years)	0.999	0.992	0.999	0.007	.999	0.999	1.00	0.055
Sex - Male	(reference)				(reference)			
Female	3.11	0.73	13.23	0.124	1.23	0.25	6.03	0.800
Ingested-to-max dose	1.14	1.10	1.19	<0.001	1.14	1.09	1.19	<0.001