Q J Med 2009; **102**:123–131
doi:10.1093/qjmed/hcn153 Advance Access publication 28 November 2008

Promethazine overdose: clinical effects, predicting delirium and the effect of charcoal

C.B. PAGE[1], S.B. DUFFULL[2], I.M. WHYTE[1,3] and G.K. ISBISTER[1,3,4]

From the [1]Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle Hospital, Newcastle, NSW, Australia, [2]School of Pharmacy, University of Otago, Dunedin, New Zealand, [3]Discipline of Clinical Pharmacology, Faculty of Health, University of Newcastle, Newcastle, NSW and [4]Tropical Toxinology Unit, Menzies School of Health Research, Charles Darwin University, Darwin, Australia

Received 8 August 2008 and in revised form 27 October 2008

Summary

Objective: The aim of this study was to describe the clinical effects of promethazine in overdose and explore the relationship between delirium and possible predictor variables.

Methods: A case series of promethazine poisonings was identified from a prospective database of poisoning admissions to a regional toxicology service. Data were extracted including demographics, details of ingestion, clinical features including delirium, complications and medical outcomes. In addition to descriptive statistics, a fully Bayesian approach using logistic regression was undertaken to investigate the relationship between predictor variables and delirium.

Results: There were 199 patients with 237 presentations, including 57 patients with 78 promethazine alone overdoses. Of these 57 patients who ingested promethazine alone the median age was 22 years [interquartile range (IQR): 17–31] and 42 were female (74%). The median dose ingested was 625 mg (IQR: 350–1250 mg). Median length of stay was 19 h (IQR: 13–27 h), ten were admitted to the intensive care unit (ICU) and four were ventilated. Delirium occurred in 33 patients (42%), tachycardia (HR>100) occurred on 44 occasions (56%) and hypotension only twice. There were no seizures, dysrhythmias or deaths. Multivariate analysis of 215 presentations (in 181 patients) where dose of promethazine ingested was known demonstrated that dose, administration of charcoal within 2 h and co-ingestants predicted whether patients developed delirium. No relationship was shown for sex and age. A plot of probability that a patient will develop delirium vs. dose was constructed which showed the probability of delirium for 250 mg was 31%, 500 mg was 42% and for 1 g was 55% for promethazine alone overdoses.

Conclusion: The main feature of promethazine toxicity is delirium, the probability of which can be predicted from the dose ingested. The administration of charcoal and the presence of co-ingestants appears to reduce the probability of delirium in a predictable manner.

Introduction

Promethazine hydrochloride is a phenothiazine derivative antihistamine first introduced in 1946 which is used in multiple medical conditions including allergic conditions, as an antiemetic and as a sedative/hypnotic agent. It is primarily a histamine (H_1) receptor antagonist but is also a direct antagonist at muscarinic (M_1) and dopamine (D_2) receptors.[1–3] In Australia promethazine is available as an over-the-counter (OTC) medication either alone as a tablet or liquid preparation or in combination with paracetamol and codeine phosphate as a syrup.

Address correspondence to Dr C.B. Page, Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, NSW 2310, Australia. email: cpage@bigpond.net.au

Promethazine alone in either formulation is rapidly absorbed after oral administration with peak concentrations after 2–3 h. It undergoes significant first pass metabolism with an oral availability of 25%. Clinical effects are seen within 20 min and its effects last 4–6 h. It is highly plasma protein bound (80–90%) with a large volume of distribution (13 l/kg) and undergoes hepatic metabolism to three main inactive metabolites which are renally excreted with only 2% of the drug excreted in its parent form.[1–4]

Reports of overdose with promethazine are predominately case reports[5–8] with only one small case series focussing on increased frequency of poisoning when promethazine was released as an OTC medication in New Zealand.[9] Promethazine in overdose appears principally to cause central nervous system (CNS) depression and anticholinergic effects, including delirium, agitation and hallucinations. There are also reports of adverse effects from therapeutic use of promethazine including dystonic reactions, psychosis in the absence of other anticholinergic symptoms or signs and neuroleptic malignant syndrome (NMS).[10–15] There is little information to assist clinicians in risk assessment and treatment of patients with promethazine overdose, including what doses are associated with significant toxicity, the time course of CNS sedation and delirium and the benefit of interventions such as activated charcoal.

We report a case series of consecutive promethazine overdoses over a 20-year period to investigate the spectrum of clinical effects of promethazine taken in overdose and also to explore the relationship between possible predictor variables and the occurrence of delirium, which we believe based on previous clinical experience to be the most important clinical feature.

Materials and methods

Setting and study design

A case series of consecutive promethazine poisoning cases was included from presentations to a large regional toxicology treatment unit which is the primary referral centre for about 300 000 people. All patients presenting with poisoning to this unit are either seen and managed in the Emergency Department (ED) by the toxicology service or seen, managed and admitted as an in-patient by the toxicology service.

Detailed data on all presentations (ED attendances and in-patient admissions) are entered into a clinical database shortly after hospital discharge.[16] The database in addition to being a quality assurance tool is also used for research purposes. Its use for retrospective reviews has previously been assessed by the Institutional Ethics Committee as an audit and has been exempted. A preformatted admission sheet for all poisoning admissions is used by medical staff to collect data[17] and this and additional information from the medical record is entered into the database by two trained personnel blinded to any study hypotheses. In addition all admissions are reviewed on a weekly basis to finalise all data collection and resolve any discrepancies. Since 1992 additional methods to improve the accuracy and minimize inconsistencies in medical chart reviews as subsequently outlined by Gilbert *et al.*[18] with the exception of formal testing of interrater agreement were also performed.

Selection of participants

All overdoses from the database between January 1987 and May 2007 were reviewed and admissions that included promethazine at any dose either as sole ingestant or with co-ingestants were extracted. All patients had a self-reported history of promethazine ingestion confirmed on at least two occasions by ED staff and the toxicology team in addition to information available from ambulance officers, family, friends and empty drug containers. Laboratory confirmation of ingestion was not routinely utilised in promethazine ingestions.

Data collection and processing

The following information was extracted from the database: patient demographic characteristics (age and sex), details of the promethazine ingestion [estimated date and time of ingestion and estimated amount ingested (mg)], co-ingested drugs (including specific classes of drugs where there were enough for analysis), clinical effects (pulse rate and blood pressure) on admission and their respective relevant maximum or minimum recording during admission, Glasgow Coma Scale (GCS) score on admission, minimum GCS score during admission, the presence of delirium (as defined by the attending Clinical Toxicologist as a rapid onset of a disturbance in consciousness accompanied by a change in cognition), outcomes or complications [seizures, dystonic reactions, neuroleptic malignant syndrome, dysrhythmias, length of stay (LOS), Intensive Care Unit (ICU) admission, mortality], and treatment (decontamination with activated charcoal, respiratory and cardiovascular support). Minor discrepancies in reported ingested dose that arose on repeated history taking were averaged prior to entry into the database, otherwise more major discrepancies in

dose were not recorded. The administration of charcoal was a clinical decision made by the attending physician at the time. A standard dose was 50 g. Cathartic use with sorbitol was routine up to 1996.

In patients who presented on more than one occasion, the following rules were applied. For those who only had multiple presentations of promethazine alone or only promethazine and co-ingestants, the first admission was used for sex and age calculation. All presentations were included to calculate other summary statistics. For those who had presentations of both ingestions of promethazine alone as well as with co-ingestants, the first promethazine alone presentation was used for sex and age calculations and subsequent promethazine alone presentations for other summary statistics. The presentations with promethazine and co-ingestants were included for other summary statistics only.

Criteria for ICU admission for patients presenting to the toxicology service are patients with a decreased level of consciousness (GCS score <9), ventilated or intubated patients and patients who require hemodynamic monitoring or circulatory support or have other major organ dysfunction requiring dedicated nursing observation. The toxicology service has a standardized discharge policy requiring review by the medical toxicology team and the psychiatry team. Both teams are available to perform reviews on a 24/7 basis.

Primary data analysis

For descriptive statistics, medians and interquartile ranges (IQR) are reported for promethazine alone as a sole ingestant and with co-ingestants. Descriptive statistics were analysed with STATA version 7 (Stata Corp., USA).

To explore the relationship between clinically important predictor variables and delirium, a logistic regression model was developed with the all the presentations where dose was known. Based on known biological plausibility the following predictor variables were considered: age, sex, promethazine dose, co-ingestants (including individual drug groups), administration of activated charcoal (at any time, <1, 2 and 4 h after ingestion) for each presentation, as well as interactions terms. Dose was considered as a covariate untransformed, as the logarithmic or in an E_{max} model or polynomial expression. The outcome variable was the occurrence of delirium.

Logistic regression models were developed using a fully Bayesian approach in WinBUGS 1.4.3. (Medical Research Council Biostatistics unit, University of Cambridge, UK), the windows interface for BUGS (Bayesian inference Using Gibbs Sampling). This is a Bayesian statistical modelling program that estimates the posterior probability distribution for the parameters of interest using Markov Chain Monte Carlo (MCMC) numerical simulation methods and can output a variety of statistics including the mean, median and credible interval from each posterior distribution. Decisions about the inclusion of covariates can be made by examining the probability distribution of the coefficients, e.g. the posterior probability that the coefficient is positive (or negative) is the area under the curve above (or below) zero. In addition, the dispersion of the distribution provides information on the strength of the data. Because this approach does not involve hypothesis testing, there are no type I error considerations with respect to each regression coefficient.

The prior probability distributions for the regression coefficients were defined by a multivariate normal distribution with mean zero and variance of 10 (relatively wide or uninformative). Model convergence was assessed by visual inspection of the overlayed chains and Gelman–Rubin diagnostics available in WinBUGS. Model selection was based on deviance information criterion[19] and the posterior probability that the covariate had a clinically significant effect on the probability of delirium. Clinical significance was determined arbitrarily as >20% difference with or without the covariate. Selection of variables was based on visual inspection of the data and univariate analysis for the dichotomous covariates. First order interaction terms were considered in the modelling process. Goodness of fit of the model was investigated by visual inspection of plots of the predicted probabilities from the logistic regression model vs. the empirical probabilities generated by binning the observed data and calculating the proportion of patients who had delirium.

Simulations from the final model in WinBUGS were used to create plots of the probability of delirium vs. dose, including separate plots for patients not given charcoal and those given charcoal, and for patients taking co-ingestants and those not. Adjusted odds ratios were estimated from the final model in WinBUGS.

Results

There were 199 patients of whom there were 237 presentations identified involving promethazine ingestion either alone or with co-ingestants. Fifty-seven of these 199 patients took promethazine alone on 78 different presentations. Table 1 outlines the clinical features, outcomes and treatment of the

Table 1 Clinical features, outcomes and treatment of patients with promethazine ingestion

	Promethazine alone		All cases	
	Patients $N=57$	Admissions $N=78$	Patients $N=199$	Admissions $N=237$
Age, year (IQR)[a]	22 (17–31)		29 (19–38)	
Sex, female (%)	42 (74)		145 (73)	
Dose ingested (IQR)		625 mg (350–1250)		500 mg (240–1175)
Tachycardia on admission (HR>100) (%)		43 (55)		119 (50)
Tachycardia during admission (HR>100) (%)		45 (58)		128 (54)
Hypotension on admission (BP<90) (%)		0 (0)		3 (1)
Hypotension during admission (BP<90) (%)		2 (3)		9 (4)
GCS < 15 (%)		44 (56)		121 (51)
GCS < 9 (%)		5 (6)		24 (10)
ICU admission (%)		10 (13)		39 (16)
Ventilation required (%)		4 (5)		26 (11)
Seizures (%)		0 (0)		3 (1)
Delirium (%)		33 (42)		71 (30)
Length of stay, hours (IQR)		19 (13–27)		19 (12–30)
Charcoal (%)		29 (37)		85 (36)

[a]All patients were >10 years with the exception of one 3 year old.

promethazine alone group in comparison to the whole group including co-ingestants. The dose of promethazine ingested was known for 181 patients who presented on 215 occasions (Table 2) which was used for the logistic regression analysis.

The median age of the 57 patients ingesting promethazine alone was 22 years [inter-quartile range (IQR): 17–31 years, range: 3–70] (Table 1). Forty-two were female (74%). The median ingested dose was 625 mg (IQR: 350–1250 mg; range: 25–2500 mg) and this was similar to the group including co-ingestants as a whole (median 500 mg, IQR: 240–1175 mg; range: 10–3000 mg). Median LOS was 19 h (IQR: 13–27 h) and 10 cases were admitted to the ICU for a reduced level of consciousness, four (5%) of which were mechanically ventilated. Reported dose ingested for the four ventilated cases was 625, 625, 1175 and 2500 mg. Median length of stay for the ICU patients was 32 h (IQR: 22–62 h).

Tachycardia (pulse rate >100 b.p.m.) occurred on 45 occasions (58%) and hypotension [systolic blood pressure (SBP) <90 mmHg) occurred only on two occasions (SBP: 88 mmHg on both occasions), both of which were brief and responded to fluids. The tachycardia was mild (pulse rate >100 and <120 b.p.m.) in 25 of the 45 occasions (56%) with the reminder between 120 and 150 b.p.m. Inotropic

Table 2 Details of the admissions included in the logistic regression analysis

	Median (IQR)	Patients $N=181$[a]	Presentations $N=215$[a]
Age, years	29 years (19–38)	–	–
Sex, female (%)	–	130 (71)	–
Dose ingested	500 mg (240–1175)	–	–
Co-ingestants (%)[a]	–	–	138 (64)
Benzodiazepine	–	–	35 (16)
Alcohol	–	–	46 (21)
TCA[a]	–	–	7 (3)
Other antihistamine	–	–	16 (7)
Opiate	–	–	26 (12)
Other antidepressant	–	–	6 (3)
Charcoal (%)	–	–	79 (37)
<1 h	–	–	11 (5)
<2 h	–	–	27 (13)
<4 h	–	–	58 (27)
Delirium (%)[b]	–	–	64 (30)

[a]Patients, presentations, co-ingestants and delirium numbers are for those where dose of promethazine ingested was known.
TCA, tricyclic antidepressant.

support was not required and there were no reported ECG changes or dysrhythmias apart from tachycardia. There were 44 presentations (56%) with an admission GCS score of <15 with only five presentations <9 (6%). Only on three occasions did the GCS fall [one point or greater (15–12, 8–6 and 6–3)] during the admission, none of which altered clinical management including disposition. Two patients had myoclonus and there were no dystonic reactions, cases of neuroleptic malignant syndrome, seizures or deaths.

In the group of patients who ingested promethazine with co-ingestants (Table 1), there were three single or multiple tonic-clonic seizures. In one patient this was due to hypoglycaemia from co-ingestants. In another patient who ingested promethazine 750 mg in addition to sertraline and pericyazine the seizure occurred 28-h post ingestion, the cause of which is uncertain. The final patient ingested promethazine 1200 mg and paracetamol 5 g and had a seizure 5-h post ingestion. Promethazine appears to be the most likely cause in this presentation. In the co-ingestant group there were no dysrhythmias apart from tachycardia or deaths.

Delirium occurred on 33 (42%) occasions with promethazine alone overdoses and 71 (30%) occasions with the group including promethazine and co-ingestants as a whole. For the group of promethazine alone presentations where dose ingested of promethazine was known, the median ingested dose for promethazine alone presentations with delirium was 875 mg (IQR: 575–1250 mg) compared with 500 mg (IQR: 200–1250 mg) in those not developing delirium. Median LOS for promethazine alone presentations with delirium was 24 h (IQR: 17–47 h) and was longer than those promethazine alone presentations without delirium with a median LOS of 17 h (IQR: 6–22 h).

Complete information on specific treatments was only available for the latter half of the 20-year period of the study (1997 onwards). In this subset, just over half (52%) of cases with delirium required a specific pharmacological treatment. Benzodiazepines with or without an antipsychotic were administered on 75% of occasions. The remaining 25% received tacrine, a long acting acetylcholine esterase inhibitor.

Univariate analysis was undertaken to explore the association between the dichotomous independent variables and the occurrence of delirium, which is presented in Table 3. This suggests that charcoal within 1 or 2 h, and any co-ingestant or benzodiazepine co-ingestant is associated with a decreased risk of delirium. However, the probability of this difference in proportions being >20% (i.e. clinically significant) is only moderate, but sufficient to be considered in the multivariate analysis.

A linear predictor model was developed with logit transformation that included up to first order interaction terms between covariates, and supported dose, charcoal within 1 or 2 h and any drug

Table 3 Details of the dichotomous dependent variables for univariate analysis including the absolute effect and the probability that this effect is significant

Probability of delirium			Difference in percent (95% credible interval)	Probability of difference		
				>0%	>10%	>20%
Sex	Female (%)	Male (%)				
	26	29	−3% (−12 to 22)	64		4
Charcoal	Nil (%)	Charcoal (%)				
<1 h	28	8	20% (−2 to 33)	97	87	59
<2 h	29	12	17% (1 to 30)	98	84	38
<4 h	29	20	9% (−6 to 22)	88	43	5
Anytime	27	25	2% (−12 to 16)	62		
Co-ingestants	Nil (%)	Co-ingestant (%)				
Any	44	19	26% (10 to 43)	100		75
Benzodiazepine	33	11	22% (8 to 33)	100	96	64
Alcohol	33	17	16% (2 to 28)	99	81	27
TCA	30	15	16% (−16 to 32)	88	73	46
Other Antihistamine[a]	29	44	−16% (−40 to 8)	–	–	–
Opiate[a]	29	38	−10% (−30 to 9)	–	–	–
Other antidepressant[a]	29	50	−21% (−56 to 15)	–	–	–

[a]Non-significant increase in risk, TCA: tricyclic antidepressant.

co-ingestion being included in the model. It was found that the logarithmic transform of dose in the covariate model provided the best fit for the data. Further analysis with specific co-ingestants demonstrated that benzodiazepine and alcohol co-ingestion were significant by themselves in univariate analysis (Table 3). Administration of charcoal within 2 h is more likely to be feasible than within 1 h, so this was retained in the final model. Plots of the probability of delirium vs. the dose ingested for the final model (i.e. adjusted) showed the increasing probability of delirium with dose, the dose-dependent decreased risk of delirium with charcoal within 2 h and the dose-dependent decreased risk with co-ingestion of particular drugs (Figure 1). For patients taking promethazine alone and not receiving charcoal, the probability that the patient will become delirious after 250 mg is 31%, 500 mg is 42% and for 1 g is 55%. The adjusted odd ratios for the effect of charcoal, co-ingestants and dose are provided in Table 4 from the final model.

To determine whether the administration of charcoal within 2 h was confounded by time of presentation to hospital (within 2 h), we undertook an analysis of a subgroup of patients presenting within 2 h which included 63 admissions, 27 who received charcoal. Eleven of 36 patients (31%) who did not receive charcoal developed delirium compared to four of the 27 patients who did receive charcoal (15%). Finally, an analysis was done with random effects included in the final model and the parameter estimates were only minimally effected suggesting that there was little over dispersion.

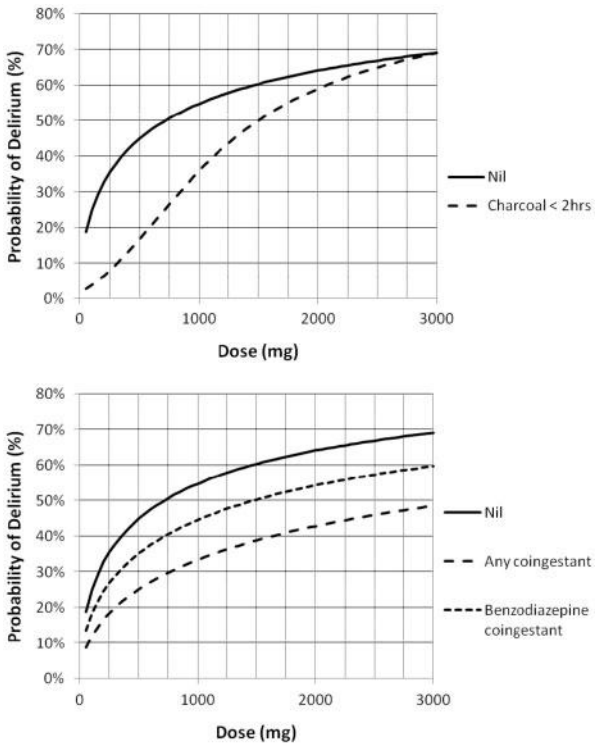

Figure 1. Plots of the mean predicted probability of delirium vs. dose for patients ingesting promethazine alone with and without charcoal (top) and for patients co-ingesting other medications (bottom).

Limitations

This study has a number of limitations. Because the study was a non-randomized retrospective analysis of data collected at the time of discharge from patient's charts, separately from any study hypotheses, detailed information that may be relevant to certain drug toxicities may not be recorded. In addition, missing data may introduce some error or bias in the results. However, entry of data in this manner allows the unbiased examination of drugs and their toxicity. A prospective study may for example allow more detailed examination of the delirium, including more accurate assessment of the onset, duration and severity. Another limitation of this study was that promethazine was not measured in plasma to confirm the history of promethazine ingestion. However, all poisoned patients admitted to having taken promethazine which was confirmed by history on at least two occasions, and confirmed by a history from ambulance officers, family and friends as well as evidence of empty drug containers. There is increasing evidence that patient reports of ingestion and the reported doses are reliable for research based on pharmacokinetic studies.[20,21]

With regards selection bias, all patients assessed and managed by the toxicology unit are either self referred or referred by their primary care practitioner. These patients are directed to our unit preferentially over attending other hospitals in our referral area, which do not have a toxicology service. Therefore, patients from the total range of intoxication are assessed and managed only by our unit. A small number of patients who are

Table 4 Adjusted odds ratios for significant variables in the final logistic regression model which included dose, charcoal given within 2 h, coingestants and an interaction term between dose and charcoal

Predictor variable	Odds ratio	Credible limits (2.5% and 97.5%)
Dose [for every log(100 mg)]	1.11	1.04–1.18
Charcoal < 2 h	0.12	0.02–0.39
Coingestants	0.43	0.21–0.78

significantly intoxicated and therefore requiring intensive care may, but not necessarily always be transferred to our unit from out of our primary referral area thus introducing a small amount of selection bias.

An important source of bias in this study was the possible misclassification of delirium, the main feature of promethazine toxicity. The diagnosis of delirium although made prospectively was made by a number of different medical staff in a non-standardised manner. However, all patients recently admitted under the toxicology service are discussed on a weekly basis and important diagnosis like delirium are discussed and finalized prior to entry into the database. This review made misclassification of the diagnosis of delirium unlikely.

Absolute dose was used in the logistic regression model rather than dose corrected for weight (i.e. mg/kg) or dose corrected for lean body weight. Although these adjustments may improve the ability of the model to predict delirium, weight (and height) is difficult to measure in the clinical environment where overdose patients are managed. As a result this makes the applicability of such a model limited in the normal clinical setting where weight and height are unlikely to be available.

The investigation of charcoal could also be biased because patients were not randomized. For example, charcoal may have been given mainly to patients with no evidence of sedation, which would immediately bias charcoal to patients with less toxicity and less probability of developing delirium. However, the time-dependent effect of charcoal suggests this did not occur, at least not in all cases. Misclassification bias of charcoal use is unlikely to be a major source of bias as it is unlikely to be administered without a written order in the patient chart. The opposite is also unlikely to occur. Lastly with respect to charcoal it was not possible to ascertain if: (i) the charcoal was completely taken and (ii) the charcoal was retained, i.e. the patient did not vomit. However, misclassification bias of charcoal use, incomplete administration and any vomiting soon after charcoal administration will only bias towards the null and reduce the apparent effect of charcoal. Doses ingested by those being given charcoal within 2 h and those not were also similar. A re-analysis of patients presenting within 2 h (i.e. able to be administered charcoal within 2 h) found a similar effect of charcoal.

Lastly, although there were no dystonic reactions reported. It is possible that this figure does not reflect the true incidence of reactions as these is often delayed and therefore may occur after discharge requiring the patient to see their primary care practitioner or attend another health care facility.

Discussion

This study demonstrates that promethazine in overdose causes CNS depression, tachycardia and delirium, the last being the most important in terms of morbidity and resource requirement. There was a consistent association between reported dose and the probability of delirium, not only for promethazine alone but also with co-ingestants. Charcoal administered within 2 h appeared to reduce the risk of delirium occurring both in patients taking promethazine alone and those co-ingesting other drugs. The co-ingestion effect appears to be due to sedation because it was significant for benzodiazepines and alcohol. The median LOS for presentations with delirium was significantly longer than the LOS for presentations without delirium reflecting the increased morbidity of delirium in overdose presentations.

There appeared to be a time-dependent effect of the administration of charcoal because administering it at increasingly shorter times did decrease the probability of delirium. For charcoal administered within 2 h the probability of delirium was reduced by ~20% in all cases or a relative risk of 0.47. It would, therefore, appear to be reasonable to offer charcoal to patients who present within 2 h if they do not have significant CNS depression. However, administration within 4 h only reduced the probability of delirium by 9% and may be an insufficient effect to warrant administration.

Delirium is the most common clinical effect of importance because of its implications for clinical care. Being able to predict the occurrence of delirium based on dose may potentially improve the initial assessment and ongoing management of patients. Tachycardia is more common but does not require any specific management as hypotension was mild and uncommon. In addition, if it was to occur it was nearly always present on admission (Table 1) so its prediction is not required. The other important clinical effects or complications such as requirement for ventilation are important and are likely to be dose-dependent. However, only four patients who took promethazine alone were ventilated, making such an analysis difficult. As in the case of tachycardia, the majority of patient's level of consciousness on admission did not deteriorate any further. Therefore, predicting the occurrence of coma/respiratory failure adds little to simple clinical observation.

With respect to promethazine alone in overdose, the extent of the CNS depression was almost always evident on presentation allowing clinical management and disposition decisions to be made at this early stage, although delirium may be initially

masked by the sedation. Larger overdoses may require intubation and ventilation for CNS depression but this was uncommon in our case series. Other CNS toxicity, e.g. dystonias, NMS and seizures were not evident in our series reflecting that these are uncommon. Tachycardia was common but was only associated with hypotension on two occasions, both of which were mild. Importantly no dysrhythmias occurred despite some massive ingestions and animal evidence of sodium channel blockade similar to class one antiarrhythmic drugs.[22] This contrasts with diphenhydramine, another commonly used antihistamine which has been reported to cause arrhythmias in overdose.[23]

Previous reports[5–14] have focussed on numerous adverse and toxicological effects from promethazine. These case reports by their nature give us a biased impression of the spectrum and/or incidence of promethazine toxicity. The one case series published to date[15] only highlighted the high morbidity, i.e. ICU admissions associated with promethazine overdose when it became available as an OTC medication and reported no other clinical effects.

Although it has not been validated the presence of delirium can be predicted from the plots of the probability of delirium vs. dose (Figure 1) which may assist in helping the treating clinician determine the resources required, including a safe location, staff utilization and appropriate pharmacological sedation if required. The co-ingestion of a sedating medication, mainly benzodiazepines and alcohol appears to reduce the risk of delirium.

In conclusion, the major clinical effect of promethazine overdose is delirium which was dose related. The risk of delirium is reduced in patients co-ingesting other drugs, in particular, the co-ingestion of benzodiazepines. Our study provides some evidence that the early administration of charcoal within 2 h may be potentially beneficial in promethazine overdose but further prospective and randomized controlled trials to validate our model are warranted to confirm this. Mild to moderate CNS depression is common but coma requiring ventilatory assistance occurs infrequently, and severe cardiovascular effects did not occur in this study.

Acknowledgements

We acknowledge Debbie Whyte and Toni Nash for data entry into the Hunter Area Toxicology Service database.

Funding

NHMRC Clinical Career Development Award (ID300785 to G.I.).

Conflict of interest: None declared.

References

1. Sharma A, Hamelin BA. Classic histamine H_1 Receptor antagonists: a critical review of their metabolic and pharmacokinetic fate from a bird's eye view. *Curr Drug Metab* 2003; **4**:105–29.
2. Strenkoski-Nix LC, Ermer J, Decleene S, Cevallos W, Mayer PR. Pharmacokinetics of promethazine hydrochloride after administration of rectal suppositories and oral syrup to healthy subjects. *Am J Health Syst Pharm* 2000; **57**:1499–505.
3. Paton DM, Webster DR. Clinical pharmacokinetics of H_1 – receptor antagonists (The antihistamines). *Clin Pharmacokinet* 1985; **10**:477–97.
4. Anonymous. Profile on Promethazine. *Aust J Pharm* 1984; **65**:114–8.
5. Shawn DH, McGuigan MA. Poisoning from dermal absorption of promethazine. *Can Med Assoc J* 1984; **130**:1460–1.
6. Leak D, Carroll D. Promethazine poisoning: Clinical and electroencephalographic observations. *BMJ* 1967; **2**:31–32.
7. Plant JR, Macleod DB. Response of a promethazine-induced coma to flumazenil. *Ann Emerg Med* 1994; **24**:979–82.
8. Cowen PJ. Toxic psychosis with antihistamines reversed by physostigmine. *Postgrad Med J* 1979; **55**:556–7.
9. Bergman J, Wallman P. Promethazine overdose: is it ''Goodnight'' after all? *NZ Med J* 1998; **111**:246–8.
10. DeGrandi T, Simon JE. Promethazine-induced dystonic reaction. *Pediatr Emerg Care* 1987; **3**:91–2.
11. Dollberg S, Hurvitz H, Kerem E, Navon P, Branski D. Hallucinations and hyperthermia after promethazine ingestion. *Acta Paediatr Scand* 1989; **78**:131–2.
12. Timnak C, Gleason O. Promethazine-induced psychosis in a 16-year-old girl. *Psychosomatics* 2004; **45**:89–90.
13. Mendhekar DN, Andrade CR. Neuroleptic malignant syndrome with promethazine. Aust. *NZ J Psychiatry* 2005; **39**:310.
14. Duggal HS. Neuroleptic malignant syndrome precipitated by promethazine and lorazepam. *Aust NZ J Psychiatry* 2001; **35**:250–1.
15. Chan-Tack KM. Neuroleptic malignant syndrome due to promethazine. *South Med J* 1999; **92**:1017–8.
16. Whyte IM, Buckley NA, Dawson AH. Data collection in clinical toxicology: are there too many variables? *J Toxicol Clin Toxicol* 2002; **40**:223–30.
17. Buckley NA, Whyte IM, Dawson AH, Reith DA. Preformatted admission charts for poisoning admissions facilitate clinical assessment and research. *Ann Emerg Med* 1999; **34(4 Pt 1)**:476–82.
18. Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart reviews in Emergency Medicine research: Where are the methods? *Ann Emerg Med* 1996; **27**:305–8.
19. Spiegelhalter DJ, Best NG, Carlin BR, van der Linde A. Bayesian measures of model complexity and fit. J R Stat Soc. *Ser B-Stat Methodol* 2002; **64**:583–616.
20. Isbister GK, Friberg LE, Hackett LP, Duffull SB. Pharmacokinetics of Quetiapine in overdose and the effect

of activated charcoal. *Clin Pharmacol and Ther* 2007; **81**:821–7.

21. Friberg LE, Isbister GK, Hackett LP, Duffull SB. The population pharmacokinetics of Citalopram after deliberate self-poisoning: A Bayesian approach. *J Pharmacokinet Pharmacodyn* 2005; **32**:571–605.
22. Tanaka H, Habuchi Y, Nishimura M, Sato N, Watanabe Y. Blockade of Na+ current by promethazine in guinea-pig ventricular myocytes. *Br J Pharmacol* 1992; **106**:900–5.
23. Sype JW, Khan IA. Prolonged QT interval with markedly abnormal ventricular repolarization in diphenhydramine overdose. *Int J Cardiol* 2005; **99**:333–5.