Bupropion poisoning: a case series

Corrine R Balit, Christa N Lynch and Geoffrey K Isbister

ABSTRACT

Objective: To investigate the toxicity of bupropion hydrochloride in deliberate self-poisoning in adults and accidental ingestion by children.

Design and setting: Prospective study of cases identified from calls to the New South Wales Poisons Information Centre (NSW PIC), with follow-up through hospital medical records.

Participants: Patients with bupropion poisoning managed in hospital, about whom the NSW PIC was contacted for advice, from 1 November 2000 to 31 July 2001 (59 adults and 10 children).

Main outcome measures: Clinical effects, adverse outcomes (including seizures and death) and treatment.

Results: 45 of the 59 adults were followed up (76%), 19 of whom had taken bupropion alone. Major clinical effects of bupropion included sinus tachycardia (83%), hypertension (56%), seizures (37%), gastrointestinal symptoms (37%) and agitation (32%). Seizures were dose-dependent, with those having seizures ingesting a significantly higher median dose ($P = 0.02$). All seizures were brief and self-limiting. 29 patients received decontamination therapy. 10 patients required pharmacological sedation, 10 were admitted to intensive care and six were intubated. None died. Eight of 10 accidental ingestions by children were followed up (80%); one child had symptoms (vomiting and hallucinations).

Conclusions: Bupropion overdose caused significant clinical effects in adults, but few in children.

MJA 2003; 178: 61–63

BUPROPION HYDROCHLORIDE (Zyban; Glaxo Wellcome Australia, Boronia, Vic.) was marketed in Australia in November 2000 in a sustained-release (SR) formulation as a short term aid in abstaining from smoking. It has previously been marketed as an antidepressant in other countries.[1] Bupropion is structurally similar to stimulants such as the amphetamines, and selectively inhibits the neuronal reuptake of dopamine and noradrenalin.[2]

Previous reports of bupropion overdose almost all involve the immediate-release (IR) formulation.[3-10] There are reports of the SR formulation in overdose,[11-14] but there is limited information on its spectrum of toxicity in overdose. Information on paediatric safety of either formulation is also limited.[15]

Immediately after bupropion was introduced in Australia, we conducted a prospective study of deliberate self-poisoning in adults and accidental poisoning in chidren with SR bupropion to investigate the toxicity of this formulation.

METHODS

Cases of bupropion poisoning were identified prospectively from calls to the New South Wales Poisons Information Centre (NSW PIC) from 1 November 2000 to 31 July 2001. NSW PIC is the only national 24-hour PIC in Australia providing poisons information to medical professionals and the general public. Cases were identified when hospitals requested advice regarding a patient with intentional or accidental bupropion ingestion.

At the time of the call, the poisons information specialist would record the patient's medical record number. A request was then sent to the medical records department of the respective hospital for a de-identified copy of the patient's record. Data collected included patient's age, sex and State where the overdose took place, relevant medical history, details of bupropion ingestion (time of ingestion, dose, co-ingestants), clinical features, investigations, decontamination therapy and treatment.

Information was extracted from the medical records by one author (C R B) using a standardised data collection form. It was assumed that there were no gastrointestinal symptoms, changes in mental status (specifically agitation, aggression or hallucinations), seizures or tremors if these were not recorded in the medical record.

Ethical approval was obtained from the ethics committee of the Children's Hospital at Westmead.

Median and interquartile range (IQR) are quoted for data not normally distributed. For comparison of two groups, the unpaired *t* test was used.

RESULTS

There were 69 cases of bupropion ingestion; 59 cases were intentional ingestions by adults and 10 were accidental ingestions by children.

Adults

Of the 59 patients who had ingested bupropion intentionally, copies of the

NSW Poisons Information Centre, The Children's Hospital at Westmead, Sydney, NSW.

Corrine R Balit, BPharm, Research Pharmacist; **Christa N Lynch,** BPharm, Senior Pharmacist; **Geoffrey K Isbister,** BSc, MB BS FACEM, Clinical Toxicologist, and Lecturer, Discipline of Clinical Pharmacology, University of Newcastle.

Reprints will not be available from the authors. Correspondence: Ms Corrine R Balit, NSW Poisons Information Centre, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145. Corrinebalit@aol.com

1: Clinical effects of bupropion overdose

Clinical feature	Bupropion alone (*n* = 19) No.	% (95% CI)	Bupropion + alcohol (*n* = 12) No.	% (95% CI)	All bupropion overdose cases (*n* = 45) No.	% (95% CI)
Tachycardia	15*	83% (59%–96%)	8	67% (35%–90%)	33‡	75% (60%–87%)
Hypertension	9†	56% (30%–80%)	5	42% (15%–72%)	21§	50% (34%–66%)
Agitation	6	32% (13%–57%)	1	8% (0.2%–38%)	13	29% (16%–44%)
Aggression	1	5% (0.1%–26%)	0	0 (0–26%)	5	13% (4%–24%)
Seizures	7	37% (16%–62%)	5	42% (15%–72%)	16	36% (22%–51%)
Hallucinations	4	21% (6%–46%)	1	8% (0.2%–38%)	6	13% (5%–27%)
Tremors	4	21% (6%–46%)	1	8% (0.2%–38%)	9	20% (10%–35%)
Gastrointestinal symptoms	7	37% (16%–62%)	5	42% (15%–72%)	15	33% (20%–49%)
Dry mouth	3	16% (3%–40%)	3	25% (5%–57%)	7	16% (7%–29%)

*Data available for 18 patients only. †Data available for 16 patients only. ‡Data available for 44 patients only. §Data available for 42 patients only.

medical records were received for 46 (78%). No details of pulse rate were recorded for one patient, and there was no blood pressure recording for three patients. One patient presented twice and only one admission was included. For 19 of the 45 patients bupropion was the only drug ingested. Alcohol was the only co-ingested substance reported in 12 patients, and the remaining 14 had taken a mixture of co-ingestants.

Median patient age was 36 years (IQR, 26–40 years) and 22 were female. The mean ingested dose was 36 tablets, or 5.1 g (SD, 4.8 g). Most cases occurred in NSW (21 of the 45 [47%]), with the remainder in other parts of Australia.

Clinical effects were similar for bupropion alone and with co-ingestants (Box 1). Comparison revealed no significant differences (data not shown).

Sixteen of the 45 patients had seizures. All were generalised tonic–clonic seizures and there were no instances of status epilepticus. Seizure duration was recorded in 10 patients; in seven, these lasted less than 30 seconds and resolved spontaneously. Seven of the 19 patients who took bupropion alone (37%) had seizures. One of these patients had a history of cerebral palsy and was excluded because of predisposition to seizures. The mean amount of bupropion ingested by the remaining six patients was 8.3 g, or 55 tablets (SD, 3.8 g), compared with 3.7 g, or 25 tablets (SD, 2.6 g), for patients who did not have seizures; this difference was significant ($P = 0.006$). Time to first seizure was recorded in four patients who had taken bupropion alone, and ranged from 2 hours 45 minutes to 8 hours (median, 5 hours). Four patients had multiple seizures; two had two, and two had three, seizures. Box 2 shows the incidence of seizures by co-ingestant and number of tablets taken.

2: Incidence of seizures for bupropion overdoses where the dose was known

Number of tablets taken	Bupropion alone No. patients	Seizure	Bupropion and non-proconvulsant drug No. patients	Seizure	All bupropion overdoses No. patients	Seizure
0–30	11	2 (18%)	14	2 (14%)	28	5 (18%)
31–60	6	3 (50%)	3	2 (67%)	10	5 (50%)
> 60	2	2 (100%)	4	4 (100%)	6	6 (100%)
Total	19	7 (37%)	21	8 (38%)	45	16 (36%)

Twenty nine of the 45 patients underwent decontamination therapy — 26 with activated charcoal and three patients had whole-bowel irrigation. Ten patients were admitted to an intensive care unit and six were intubated. There were no deaths. Ten patients received a benzodiazepine or an antipsychotic (or both) for sedation, three patients received an antiemetic, two patients received phenytoin as seizure prophylaxis, and one patient received magnesium for a prolonged QT interval corrected for heart rate (QTc). There were no cases of hypotension or arrhythmias (apart from tachycardia).

Children

Medical records were received for eight of the 10 cases (80%) of accidental ingestion by children. In all cases bupropion was the only drug ingested. The children were aged between nine months and five years (median, 2.5 years). The number of tablets ingested ranged from three-quarters of a tablet to two tablets. Weight of the child was known in six cases, and the dose per weight ranged from 7 mg/kg to 19 mg/kg. Three children received activated charcoal. Only one child was symptomatic after ingesting one tablet. This child vomited one hour after ingestion and experienced hallucinations, although the time frame for the hallucinations in relation to time of ingestion was uncertain. The symptoms resolved without any intervention.

DISCUSSION

Bupropion SR overdose caused significant effects, including seizures, in over a third of cases. Other common effects in the 19 patients who took bupropion alone included tachycardia (83%), hypertension (56%), agitation (32%)

and gastrointestinal symptoms (37%). These findings are consistent with a previous study of the IR formulation in 58 patients,[10] with the only significant differences from our findings being lower rates of tachycardia (43%) and gastrointestinal symptoms (14%) with the IR formulation.

Seizures occur in both therapeutic doses and overdose of bupropion. The risk of seizures associated with therapeutic use of the SR formulation is 0.1% with doses of no more than 300 mg per day.[2] In overdose, the incidence of seizures has previously been reported to occur in a third of cases with the IR formulation.[16] Our study suggests a dose-dependent relationship with seizures, where patients ingesting more than 30 tablets were more likely to have a seizure, and nearly all patients ingesting more than 60 tablets had a seizure. Most seizures resolved spontaneously, often before a benzodiazepine was given.

Early studies of bupropion suggested it was less cardiotoxic than other antidepressants, and this was supported in the study of overdoses with the IR formulation.[10] More recently, two cases were reported suggesting cardiotoxicity based on a prolonged QTc.[3,7] In our study the major cardiovascular effects were tachycardia and mild hypertension, with no patient having arrhythmias or hypotension, although one was treated for a prolonged QTc. There were no other reported cardiac effects in this patient, including arrhythmias other than tachycardia.

There is limited information on accidental paediatric ingestion of bupropion. A study of 114 children showed that 92% were asymptomatic, with most children taking less than two tablets.[15] Our study supports this, with only one child becoming symptomatic.

Our study was limited by the need for clinical details to be extracted from medical records. Although the investigator was not blinded during this process, a standardised extraction process was used to collect predetermined data. Recruiting only patients where hospitals contacted the PIC for advice might introduce a bias towards severe cases. However, we began this study as soon as bupropion was introduced into Australia, so that information on the effects of overdose was not widely available. Sixty-three per cent of patients who experienced seizures had been reported to the NSW PIC before their seizure occurred, supporting our contention that cases were being reported regardless of severity.

The mainstay of treatment for bupropion overdose is supportive care.[2] Patients should be given activated charcoal if they present soon after the ingestion.[17] Our study demonstrates the importance of recognising the potential for deliberate self-poisoning, as well as accidental paediatric ingestions, of any drug before it is marketed.

ACKNOWLEDGEMENTS

We would like to thank all the staff at the NSW Poisons Information Centre for their assistance with recruiting the cases. We would also like to thank Linda Graudins, Keith Edwards, Nick Ryan, Gerard O'Reilly, Kent McGregor and Kevin Humprey for their assistance with the cases at their respective hospitals.

COMPETING INTERESTS

None identified.

REFERENCES

1. Preskorn SH, Othmer SC. Evaluation of bupropion hydrochloride: the first of a new class of atypical antidepressants. *Pharmacotherapy* 1984; 4: 20-34.
2. Product information: Zyban — sustained release tablets. Boronia, Vic.: Glaxo Wellcome Australia, 2000.
3. Paris PA, Saucier JR. ECG conduction delays associated with massive bupropion overdose. *J Toxicol Clin Toxicol* 1998; 36: 595-598.
4. Gittelman DK, Kirby MG. A seizure following bupropion overdose. *J Clin Psychiatry* 1993; 54: 162.
5. Storrow AB. Bupropion overdose and seizure. *Am J Emerg Med* 1994; 12: 183-184.
6. Friel PN, Logan BK, Fligner CL. Three fatal drug overdoses involving bupropion. *J Anal Toxicol* 1993; 17: 436-438.
7. Shrier M, Diaz JE, Tsarouhas N, Johnson RW. Cardiotoxicity associated with bupropion overdose. *Ann Emerg Med* 2000; 35: 100.
8. Harris CR, Gualtieri J, Stark G. Fatal bupropion overdose. *J Toxicol Clin Toxicol* 1997; 35: 321-324.
9. Ayers S, Tobias JD. Bupropion overdose in an adolescent. *Pediatric Emerg Care* 2001; 17: 104-106.
10. Spiller HA, Ramoska EA, Krenzelok EP, et al. Bupropion overdose: a 3-year multi-center retrospective analysis. *Am J Emerg Med* 1994; 12: 43-45.
11. Harmon T, Kurta D, Krenzelok EP. Delayed seizures from sustained release bupropion overdose. *J Toxicol Clin Toxicol* 1998; 36(5): 522.
12. Weiner A, Nowicki T, Bayer M, McKay C. Zyban (bupropion) overdose. *J Toxicol Clin Toxicol* 1998; 36: 521.
13. Bhattacharjee C, Smith M, Todd F, Gillespie M. Bupropion overdose: a potential problem with the new "miracle" anti-smoking drug. *Int J Clin Practice* 2001; 55: 221-222.
14. Paoloni R, Szekely I. Sustained-release bupropion overdose: a new entity for Australian emergency departments. *Emerg Med* 2002; 14: 109-112.
15. Shepherd G, Velez LI, James DK, Keyes DC. Pediatric bupropion exposures reported in Texas: 1998 - 1999. *J Toxicol Clin Toxicol* 2001; 39: 263.
16. Wellbutrin. In: Dowd AL, Schummacher MM, editors. Physicians desk reference. Montvale, NJ: Medical Economics Data, 1993: 842-844.
17. American Academy of Clinical Toxicology, European Association of Poison Centres and Clinical Toxicologists. Position statement: single-dose charcoal. *J Toxicol Clin Toxicol* 1997; 35: 721-741.

(Received 29 Apr 2002, accepted 9 Oct 2002) ❑