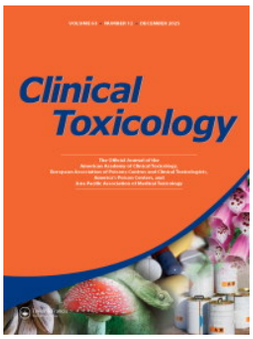

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POISON CENTRE RESEARCH

Gastrointestinal decontamination by gastroscopy in massive bupropion overdoses

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ABSTRACT

Introduction: Overdoses of the atypical antidepressant bupropion are increasing. Management of very large ingestions is challenging, as severe and treatment-refractory circulatory compromise is not uncommon. In this context, limiting absorption is appealing. Modified-release bupropion tablets maintain their shape during dissolution and are too large for gastric lavage. Although endoscopic evacuation has been described, it remains unclear whether clinically-significant amounts of pharmacologically active substance can be recovered.

Methods: In this case series of six patients with bupropion overdoses exceeding 10 g, gastroscopic evacuation was performed, and the recovered material was analyzed to quantify bupropion content.

Results: When gastroscopy was performed within 6 h of ingestion, recovered amounts of bupropion ranged from 3,414 mg to 5,926 mg. When the time to gastroscopy exceeded 24 h, retrieved amounts were much smaller, ranging from 92 mg to 296 mg.

Discussion: The patients in this series can be divided into two groups based on intervention timing. In the early intervention group (gastroscopy performed within 6 h of ingestion), the amount of bupropion recovered was, in all cases, sufficient by itself to cause clinically significant intoxication. Gastroscopic removal was therefore likely to have been clinically relevant.

Conclusions: In massive bupropion overdoses, gastroscopy can remove clinically relevant amounts of drug if performed within 6 h of ingestion. After 24 h, tablets may still be recovered, but the pharmacological content was minimal. Computed tomography imaging correlated well with tablet recovery and may be useful in selecting cases suitable for gastroscopic intervention.

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Bupropion overdose; extended-release; gastrointestinal decontamination; gastroscopy; modified-release

Introduction

Bupropion is an atypical antidepressant that inhibits the reuptake of dopamine and noradrenaline. Reports of single-substance bupropion exposures in the United States National Poison Data System® have increased steadily over the past decade, and by 2020–2021, it was the antidepressant most often associated with severe outcomes [1]. A similar pattern is evident in Sweden, where prescriptions have risen by 62% in five years, paralleled by a 118% increase in calls to the Swedish Poisons Information Centre regarding bupropion exposures [2].

Bupropion has a narrow therapeutic index, and seizures may occur even after an unintentional doubling of the prescribed dose [3]. In overdose, seizure risk increases in a dose-dependent manner and at higher doses, it can cause recurrent seizures, QRS complex prolongation, dysrhythmias and circulatory collapse [4–7].

Management is mainly supportive, and there is no specific antidote. Cardiac toxicity may be severe, and because QRS complex prolongation appears to result from myocardial gap-junction blockade rather than sodium channel inhibition, sodium bicarbonate is typically ineffective [8,9]. Lidocaine has been reported to reverse dyrhythmias in isolated cases, but in patients with severe intoxications conventional supportive measures often fail to prevent cardiovascular collapse [10–12]. In several patients, veno-arterial extracorporeal membrane oxygenation has been required as a bridge to survival [10,13,14].

Given these risks and limited treatment options, strategies to reduce absorption of ingested tablets are

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theoretically attractive. Gastric lavage will not work here because the modified-release tablets used in Sweden (marketed as XL in the United States) are too large to be retrieved using standard lavage tubes [15].

In a few reported cases of bupropion overdose, tablets have been successfully removed by gastroscopy [16–18]. Furthermore, modified-release bupropion tablets have been documented in the stomach at autopsy, strongly arguing for more intensive gastrointestinal decontamination [19,20].

Quantifying the amount of drug retained in the stomach could help evaluate the potential effectiveness of gastroscopic evacuation. Post-mortem studies unrelated to bupropion have shown that pharmacobezoars can contain large amounts of drug, and in one pediatric quinidine poisoning, high concentrations were found in gastric aspirate prior to bezoar removal by gastroscopy [21–23]. In most published cases of gastroscopic removal of modified-release tablets, including two involving bupropion, it has not been demonstrated whether any active substance was removed or if the outcome was affected by the intervention [16,18,24–29]. In an attempt to gain clearer evidence, we present a non-consecutive case series of bupropion overdoses in which gastroscopic evacuation was performed, with the retrieved tablets subsequently analyzed to determine their bupropion content.

Methods

Study design and setting

This was a retrospective case series of patients with massive bupropion exposures in which the Swedish Poisons Information Centre was consulted. The Swedish Poisons Information Centre is a national service that provides 24 h toxicological advice to both the general public (population 10.5 million) and healthcare professionals. The centre receives more than 110,000 calls annually, of which approximately 40% originate from hospitals. Ethical approval, including waiver of consent, was granted by the regional ethics review board in Stockholm (D.nr. 2023-06256-01). Language editing assistance was provided using an AI-based language tool (ChatGPT 5, Open AI). The tool was used solely to improve clarity and style. All data, interpretations and conclusions are entirely the work of the authors.

Selection of patients

At the Swedish Poisons Information Centre, a bupropion exposure is provisionally classified as "massive" if the estimated amount exceeds 10 g or 150 mg/kg, as such doses are considered to carry a clinically significant risk of hemodynamic compromise. Beginning in 2022, the Swedish Poisons Information Centre has routinely recommended performing low-dose abdominal computed tomography in such cases. If computed tomography confirms the presence of tablets corresponding to this threshold, and a substantial proportion remains in the stomach, a gastroscopic evacuation is recommended.

This case series represents a convenience sample of patients from 2022 to 2024 in whom gastroscopic evacuation was performed and evacuated tablets were made available for analysis at the Swedish Medical Products Agency laboratory via the Swedish Poisons Information Centre.

Laboratory methods

Evacuated tablets were allowed to dry in a desiccator containing silica gel sorbent. Once dried, the tablets were weighed and ground to a fine powder in a mortar. Aliquots of the powder were accurately weighed into sample tubes, and an internal standard, 1,4-bis(trimethylsilyl)benzene (patients 1–4) or maleic acid (patients 5 and 6), with known assay, was also weighed into each tube. Approximately 1 mL of deuterated methanol (99.8% atom-D) was then added to each tube, followed by vortexing for 30 sec, ultrasonication for 15 min and centrifugation at 2,500 rpm for 5 min. The supernatant was then transferred into a 5 mm nuclear magnetic resonance (NMR) tube, and a quantitative ^{1}H-NMR experiment was performed on a 600 MHz Bruker Avance III HD NMR instrument equipped with a cryogenically cooled probe. The resulting NMR spectra were integrated, and signals from bupropion were correlated to the internal standard signals and quantified.

Blood concentrations of bupropion and hydroxybupropion were measured using liquid chromatography-tandem mass spectrometry. Samples were collected at the time of gastroscopy, and in two cases, repeated 12 h later. The analyses were performed at a reference laboratory, and results were not available in real time to guide clinical management.

Data collection

The clinical course was followed by a poison centre physician through repeated telephone contacts, and relevant clinical details were recorded. After case completion, medical records were requested from the treating hospitals.

Data analysis

All data are presented descriptively due to the small number of cases and observational nature of this case series.

Results

Six patients with reported ingestions ranging from bupropion 13.5 g to 35 g were included (Table 1). All patients were endotracheally intubated and mechanically ventilated in the intensive care unit. Three patients had seizures prior to endotracheal intubation. Four had prolonged QRS complex duration (>100 msec) at some time during the course. All patients received activated charcoal after gastroscopy. Two patients were transferred to extracorporeal membrane oxygenation centres but never required veno-arterial extracorporeal membrane oxygenation, while one patient required veno-arterial

Table 1. Recovered doses of bupropion hydrochloride in relation to reported intake and time to gastroscopy.

Patient	Reported intake (g)	Reported tablet strength (mg)	Time to gastroscopy (h)	Number of recovered tablets	Total amount of bupropion recovered after gastroscopy (mg) and remaining amount of bupropion per retrieved tablet [%]	Blood concentrations (µg/L) and time post-overdose (h)	Clinical course	Endotracheal intubation (days)
1	18	300	4	29	5,926 [68]	Bupropion 940 (4), hydroxybupropion 1,800 (4) Bupropion 230 (16), hydroxybupropion 3,100 (16)	Endotracheally intubated for gastroscopy; transferred to extracorporeal membrane oxygenation centre after procedure. Remained stable, never canulated. Maximal QRS complex duration of 90 msec.	1.5
2	15	150	6	54	3,535 [44]	Bupropion 440 (6), hydroxybupropion 1,300 (6) Bupropion 160 (18), hydroxybupropion 1,200 (18)	Endotracheally intubated after repeated seizures. Maximal QRS complex duration of 114 msec.	1
3	13.5	150	6	69	3,414 [33]	Not available	Endotracheally intubated for gastroscopy. Maximal QRS complex duration 96 msec.	1
4	Not available	150 + 300	24	30	225 [2.5-5]	Bupropion 770 (26) hydroxybupropion 5,600 (26)	Endotracheally intubated after repeated seizures. Ventricular tachycardia responding to lidocaine. Maximal QRS complex duration 184 msec. Transferred to extracorporeal membrane oxygenation centre but never canulated.	3
5	30	150 + 300	26	30	92 [1–2]	Bupropion 850 (21), hydroxybupropion 2,700 (21)	Endotracheally intubated after repeated seizures. Maximal QRS complex duration 123 msec.	3
6	Not available	150	34	210	296 [1]	Bupropion 790 (34), hydroxybupropion 3,100 (34)	Endotracheally intubated due to Glasgow Coma Scale 3. Pronounced hypotension. Veno-arterial extracorporeal membrane oxygenation after cardiac arrest 18 h after admission. Maximal QRS complex duration 140 msec.	6

Therapeutic concentrations of bupropion are 50–100 µg/L. Patient 6 is described in greater detail in [17].

extracorporeal membrane oxygenation due to circulatory collapse. The duration of endotracheal intubation ranged from 1 day to 6 days. All patients survived and were discharged from the intensive care unit.

Overall, the time from ingestion to gastroscopy ranged from 4 h to 34 h, determined by the interval to presentation, the time required to identify the ingested substance, and the timing of consultation with the Swedish Poisons Information Centre (Table 1). Based on intervention timing, the patients can be differentiated into two groups.

In the early intervention group ($n = 3$), all patients underwent computed tomography and gastroscopy within 6 h of ingestion, and tablets were clearly visible on computed tomography (Figure 1); gastroscopy recovered substantial amounts of bupropion, ranging from 3,414 mg to 5,926 mg.

In the delayed intervention group ($n = 3$), gastroscopy was performed ≥24 h after ingestion, only one patient underwent computed tomography (24 h after ingestion), and the amounts of bupropion recovered were much smaller, ranging from 92 mg to 296 mg.

Discussion

To our knowledge, this is the first case series in which gastroscopic removal of modified-release bupropion (XL) tablets has been evaluated by laboratory analysis of the evacuated material. Our study provides an important perspective by quantifying the drug content of recovered tablets, complementing earlier reports in which the outcome of the interventions was primarily described in terms of the number of tablets removed [16,18,25,27–29].

The patients in this series can be divided into two groups based on intervention timing. In the early intervention group, the amount of bupropion recovered was, in all cases, sufficient by itself to cause clinically significant intoxication. Gastroscopic removal was therefore likely to have been clinically relevant. None of these patients developed dyrhythmias, and only one had a QRS complex duration greater than 100 msec during the course.

In contrast, the delayed intervention group yielded only small amounts of active drug, with most recovered material consisting of empty casings or "ghost pills" [30]. All patients in this group had clinically significant QRS complex prolongation; all three were treated with magnesium, and two with lidocaine for a ventricular dyrhythmia. One required veno-arterial extracorporeal membrane oxygenation due to circulatory collapse. These observations suggest that while late gastroscopy can retrieve residual pill material, it is unlikely to meaningfully reduce toxic load or alter the clinical course.

Computed tomography imaging proved highly useful as a screening tool in the early intervention group, with excellent concordance between computed tomography findings and tablet recovery. Modified-release bupropion (XL) consists of a densely compressed core of bupropion salt encased in a water-permeable polymer membrane [31]. Dissolution occurs as gastrointestinal fluids penetrate the membrane and gradually dissolve the core, leaving empty casings that are excreted in the stool. We postulate that computed tomography primarily visualizes the intact drug core, while emptied shells are less radiopaque. Notably, in one delayed-intervention patient (patient 5), computed tomography revealed no intragastric tablets (Figure 2), yet 30 empty casings were recovered at gastroscopy.

As no gastroscopies were performed between 6 h and 24 h after ingestion, the amount of recoverable drug in this interval remains unknown. The extent of loss of active substance from the tablets recovered in

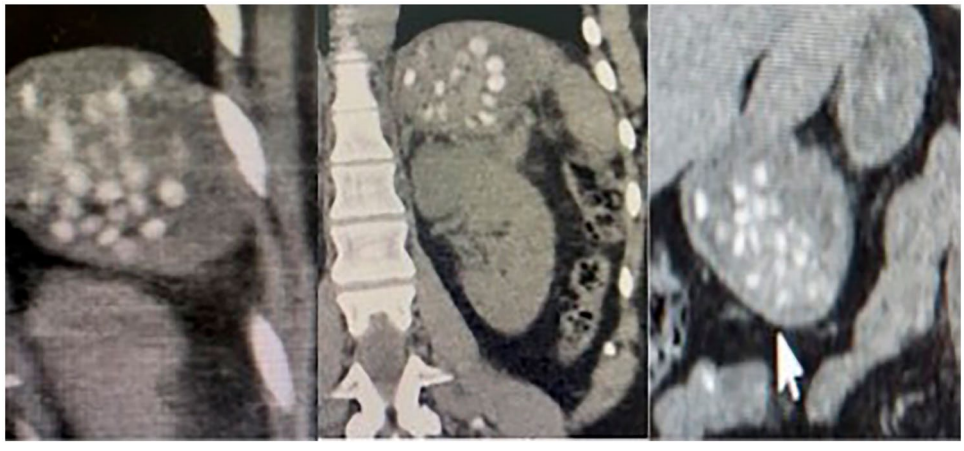

Figure 1. Computed tomography of the abdomen in the three patients where it was performed within 6 h of overdose.

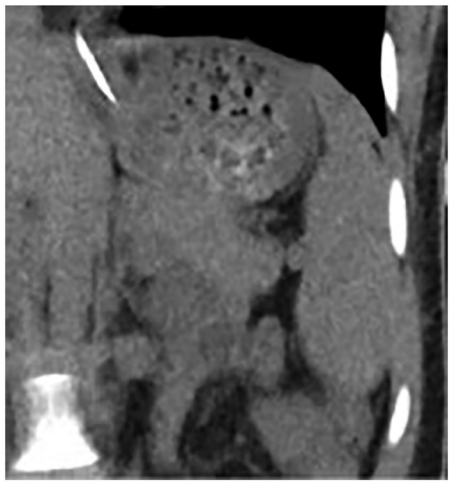

Figure 2. Computed tomography of the abdomen performed 24 h after overdose in patient 5.

the early intervention group suggests that dissolution in overdose does not differ substantially from dissolution under therapeutic dosing, in which blood concentrations peak at around 6 h and tablets are designed to release fully within 16 h according to United States Pharmacopeia dissolution standards [4,32]. No pharmacobezoar formation was observed in any of our cases, a finding that further supports rapid dissolution.

Evacuation of tablets by gastroscopy is not without risk. The procedure is resource-intensive and may cause mechanical trauma. Determining when the potential benefits outweigh these hazards remains challenging. In this study, we applied a threshold of >10 g (or 150 mg/kg), based on the assumption that such doses may carry a risk of circulatory failure requiring veno-arterial extracorporeal membrane oxygenation. Whether this threshold is appropriate remains to be established.

We suggest that low-dose abdominal computed tomography in cases of suspected large bupropion ingestions may be useful not only to determine whether gastroscopic removal is indicated, but also to guide a decision on whether to transfer high-risk patients to facilities with veno-arterial extracorporeal membrane oxygenation capability. In some cases, tablets may already have passed into the small intestine, where they are no longer amenable to gastroscopic removal but still provide an indication of the extent of intoxication.

A strength of this study is that all bupropion formulations marketed in Sweden for major depression are modified-release tablets employing the same system, making our findings generalizable across different manufacturers. The main limitation of this case series is its observational design and the small number of patients included, which render all conclusions tentative. In addition, the results should not be extrapolated to other modified-release systems as these likely behave differently after ingestion. While co-ingestion of other substances (quetiapine and/or promethazine) was suspected in four patients (patients 1,2,4, and 6), this may have influenced the clinical courses but is unlikely to have affected the dissolution rates of the bupropion tablets.

Conclusions

Our findings suggest that gastroscopic evacuation of modified-release bupropion (XL) tablets may be clinically valuable if performed early, but appears futile 24 h or more after ingestion. Abdominal computed tomography may be a useful adjunct in the early assessment of these patients. Further work is needed to better delineate the time window during which gastroscopic removal remains meaningful.

Disclosure statement

No potential conflict of interest was reported by the authors.

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