Ten Years of Robotripping: Evidence of Tolerance to Dextromethorphan Hydrobromide in a Long-Term User

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Abstract

Introduction Dextromethorphan hydrobromide is widely available as an over-the-counter cough suppressant. A semi-synthetic opioid displaying *N*-methyl-D-aspartate receptor antagonism, it is commonly abused for recreational purposes. Spuriously elevated serum chloride concentrations are a well-described phenomenon in the setting of dextromethorphan hydrobromide toxicity, but evidence to suggest the development of tolerance is limited to case reports.

Case A 32-year-old male known to chronically ingest dextromethorphan hydrobromide for recreational purposes presented to regional hospitals on 179 occasions over 110 months and was treated for dextromethorphan toxicity on 163/174 (93.7%) of these visits. He reported a subjective need to increase his dosing over time to achieve the same degree of intoxication. Measured serum chloride over this period ($n = 217$) ranged from 98 to 138 mEq/L (median 115 mEq/L, IQR 110–123 mEq/L). Measured concentrations over the 110-month period progressively rose, with a fitted plot of $111.15 + 0.00232x$ describing the rise in measured chloride. Though not formally assessed, anion gaps tended to become progressively more negative over the observed period.

Discussion We report a patient with persistent dextromethorphan hydrobromide abuse at escalating doses whose mean serum chloride concentration increased, on average, by 0.00232 mEq/L every day over a 110-month period. This case demonstrates progressive spurious hyperchloremia secondary to bromide interference in hospital-based chloride assays, supporting the patient's reported need to dose escalate to the same desired effect. Although this artefactual laboratory finding is a well-documented result of bromide ingestion, it may be useful in identifying patterns of dextromethorphan hydrobromide use that suggest tolerance.

Keywords Dextromethorphan · Bromism · Robotripping · Hyperchloremia · Tolerance

Introduction

Dextromethorphan hydrobromide (DXM HBr) is a semi-synthetic opioid sharing *N*-methyl-D-aspartate receptor

antagonistic properties with its primary metabolite, dextrorphan, but lacking significant analgesic properties. It is available over the counter and is commonly used recreationally for its NMDA receptor antagonism and dissociative effects [1–4]. Its recreational abuse is common, with 44,206 DXM HBr abuse cases called to accredited Poison Centers between 2000 and 2010 [5]. This likely underestimates the prevalence of recreational dextromethorphan use, inasmuch as only those cases that are called in to Poison Centers are accounted for in this data.

Neither tolerance nor dependence has been clearly established in dextromethorphan users, although case reports of dependence exist [6]. It is possible that chronic dextromethorphan use and the subsequent development of tolerance may lead to escalating doses [6], analogous to the development of tolerance to other substances of abuse [7, 8]. This may theoretically be demonstrated by a spurious increase in

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measured serum chloride when serum bromide interferes with susceptible ion-selective chloride assays [9]. Herein, we describe a patient who frequently presented to regional emergency departments (EDs) following repeated use of DXM HBr formulations.

Case History

A 32-year-old male with a known history of chronic, persistent dextromethorphan use and comorbid diagnoses of depression, antisocial personality disorder, and tobacco and ethanol use disorders presented to the emergency departments of five urban health care systems on at least 179 separate occasions over a 110-month period, frequently evidencing excessive serotonergic tone, with a clinical diagnosis of serotonin syndrome reported on 8 individual visits to a single hospital for which complete notes were available for review. Of these, he was admitted on 127 unique occasions. He reported chronically escalating doses of DXM HBr in order to achieve his desired degree of intoxication and verified this with one author (SS) on multiple visits, including at least one episode of care in which he was evaluated by a medical toxicologist and deemed to be without clinical signs of intoxication.

After obtaining informed consent from the patient for publication of this case report, episodes of care were retrospectively identified via a unified electronic medical record system (Epic®, Verona WI); these were cross-referenced with patient records from a regional Poison Control System database (Toxicall®). A single author (TO) abstracted all measured serum chloride concentrations from the patient's medical record and identified additional episodes of care within Toxicall® not identified on medical chart review. A clinical diagnosis of substance use, intoxication, or abuse was assigned to each episode of care based on hand review of medical provider notes, where available, and discharge diagnoses referencing dextromethorphan. Those without diagnoses or medical provider notes specifically noting dextromethorphan exposure were coded as unrelated to dextromethorphan. Serum chloride concentrations were coded for hospital day in order to assess serum chloride trends over the course of the patient's hospitalization. All data analysis was performed using Stata/IC® (version 15.1, College Station, TX).

A clinical diagnosis of dextromethorphan abuse, overdose or toxicity, “drug abuse,” or chemical dependency was made on 163 of 174 visits (93.7%). Additional presenting diagnoses included unknown (8/174, 4.60%), assault, and psychosis (1/174, 0.58% each). Serum chloride concentrations were measured 217 times, including 84 repeat measurements taken during the same hospital stay (Table 1). Serum chloride concentrations were not obtained for all presentations adjudicated as related to DXM HBr exposure. On 48 presentations,

chloride was not measured on the day of admission, although in some cases it was subsequently measured.

Over 110 months, the patient's serum chloride concentrations ranged from 98 to 138 mEq/L (median 115 mEq/L, IQR 110–123 mEq/L). In general, serum chloride concentrations tended to be higher on the date of presentation, decreasing over the hospitalization course (Fig. 1). The distribution of initial serum chloride concentrations (Fig. 2) largely mirrored the distribution of chloride concentrations measured on presentations in which physicians made a clinical diagnosis of dextromethorphan abuse, overdose or toxicity, “drug abuse,” or chemical dependency. Serum chlorides differed significantly between episodes of care for dextromethorphan abuse, overdose or toxicity, “drug abuse,” or chemical dependency and those in which other diagnoses were made (Mann-Whitney test $z = -2.908$, $p = 0.0036$), as did mean presenting chloride concentrations (119.0 mEq/L versus 110.4 mEq/L, respectively, $p = 0.0022$). Neither analysis was statistically affected when all serum chlorides, including those occurring after the initial blood draw, were included. Dextromethorphan was not quantitatively measured; however, urine confirmatory mass spectrometry identified dextromethorphan or its metabolites on 10/14 testing occasions. Numerous additional urine toxicology screens reported positive phencyclidine and opiate assays, two assays known to be affected significantly by cross-reactivity with dextromethorphan [10, 11].

A scatterplot of chloride concentrations demonstrated an upward trend in serum chloride concentrations over time, confirmed by linear regression, with a calculated fit line of $111.15 + 0.00232$ (date) (Fig. 3a). In other words, for every day past the initial presentation on 03 July 2009 until the last presentation on 19 August 2018, the predicted serum chloride increased by 0.002 32 mEq/L. Results were similar when serum chloride concentrations following the initial (presenting) bloodwork were excluded, although R^2 of the regression model increased from 6.4 to 20.2% (Fig. 3b). While not formally assessed, serum anion gaps tended to be low on presentation, to become progressively more negative over the entire observation period, and to normalize while hospitalized.

Discussion

Dextromethorphan is found in multiple formulations and is widely available as a hydrobromide salt. Similar to phencyclidine and ketamine, dextromethorphan and its primary active metabolite, dextrorphan, antagonize *N*-methyl-D-aspartate (NMDA) receptors [12, 13]. Presynaptic serotonin reuptake inhibition, more so by the parent compound than by metabolites, may produce the serotonin syndrome, while activity at the sigma receptor may further produce a phencyclidine and

Table 1 Serum chloride concentrations by day of hospitalization

Hospital day	Total	Admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 12	Day 14
All measurements (<i>n</i>)	217	156	36	7	4	2	3	1	2	1	3	1	1
Mean (mEq/L)	116.5	118.7	114.4	110.1	106.8	102.5	105.3	101	100.5	103	104	110	102
Unrelated to drug use	14	7	2	0	0	0	0	0	0	0	3	1	1
Mean (MmEq/L)	108.5	110.1	112	.	.	.	.	.	.	.	104	110	102
Related to drug use	203	147	35	8	4	2	3	1	2	1	0	0	0
Mean (mEq/L)	117	119.1	114.5	110.1	106.8	102.5	105.3	101	100.5	103	.	.	.

ketamine-like dysphoria [6, 14]. The measured serum hyperchloremia common to dextromethorphan overdose has previously been described as a false elevation due to interference in the measurement of serum chloride concentration by the hydrobromide moiety, due to incompletely selective anion electrodes or to variability in the selectivity of anion specificity among employed reagents [9, 15–19]. Similar spurious chloride elevations have been previously reported during the use of other prescribed bromide salts [12, 20]. Chloride analyzers are affected variably by the presence of bromide ions [19], the presumed variability in chloride analyses over 10 years of presentations to different hospital systems likely impacted the reported serum chloride concentrations. Taken together, the progressive measured hyperchloremia supports the supposition that serum chloride trends over time may serve as markers of increasing dextromethorphan use due to tolerance.

Data from the American Association of Poison Control Centers' National Poison Data System (NPDS) confirm that dextromethorphan use is prevalent, particularly in adolescent and young adult populations [21], and use appeared to plateau in 2006 [5]. Despite this, objective evidence of dextromethorphan dependence and tolerance is limited. A single case of

reported dextromethorphan dependence is limited in scope [22], while one additional case [6] provides a narrative description of dextromethorphan withdrawal symptoms and reported escalating doses without evidence of progressive hyperchloremia. In this case, we offer evidence of progressively increasing hyperchloremia on presentation, supporting the patient's report of chronic dose escalation and suggesting tolerance and dependence. Diminution of hyperchloremia over periods of hospitalization provides collateral evidence of recurrent dextromethorphan hydrobromide overdose, with spurious hyperchloremia resolving once the patient was sequestered from repeated exposures. Results of linear regression suggest that the patient's persistently worsening hyperchloremia was unlikely due to chance alone.

This laboratory demonstration of a single patient's falsely elevated and increasing serum chloride concentration over multiple ED visits related to dextromethorphan hydrobromide has face validity, but has not previously been evaluated in as large a single patient case experience nor in larger multipatient series. Nonetheless, spurious hyperchloremia is well-documented in the setting of other forms of bromism, both in cases of subtoxic bromide exposures [23] and in cases of acute exposure [16]. Indeed, bromide interference on a single ion-selective electrode

Fig. 1 Median serum chloride by hospitalization day

Fig. 2 Distribution of serum chloride concentrations

has been previously found to occur at serum concentrations above 2.0 mmol/L [18]. This patient's experience, with

progressive hyperchloremia defervescing over periods of hospitalization, is compelling both in theory and by statistical

Fig. 3 **a** All serum chloride concentration over time. **b** Presenting serum chloride concentrations over time

Fig. 3 continued.

evaluation that dose escalation was occurring. Taken with the patient's reported escalation in DXM HBr doses, dextromethorphan tolerance is a unifying etiology explaining this single patient's experience over 100 months. Further study, including the prospective evaluation of additional patients who chronically misuse dextromethorphan, may establish a clearer link between chronic use and tolerance.

Nonetheless, it is plausible that the observed hyperchloremia was not spurious, but rather due to one of many known causes of hyperchloremia. Although access to complete medical records from all systems in which the patient received care was not available, we feel that this is unlikely in this patient, whose persistent low or negative anion gap further supported bromism in the context of a strong history of DXM HBr abuse. Clear reports of chronic persistent DXM HBr abuse were not accompanied by suggestions of other causes of true hyperchloremia, such as persistent toluene abuse or other etiologies of renal tubular acidoses, exogenous chloride administration, or persistent diarrhea. Available chart review did not indicate overzealous crystalloid repletion as a likely etiology of iatrogenic hyperchloremia, and the patient was not known to be prescribed carbonic anhydrase inhibitors, such as topiramate or acetazolamide. It is also theoretically possible, albeit unlikely, that the patient's hyperchloremia was, in fact, due to excess chloride intake. Little, if any, evidence of expected concurrent electrolyte findings was present to support another exposure (no consistent, concurrent hyponatremia to suggest ongoing sodium chloride exposure, for example).

Despite compelling evidence, this case offers but a narrow window into an aspect of dextromethorphan abuse that has previously been addressed in little more than a cursory manner. Thus, limitations to the analysis of this case exist. Chief among them, although the patient's history over 10 years remained consistent and he underwent multiple confirmatory urine drug tests verifying the presence of the reported ingestion, no quantitation of dextromethorphan exists in the patient's chart. Nonetheless, we feel that 10 years of consistently reported dextromethorphan ingestions, coupled with a toxidrome consistent with this exposure over a large number of presentations, and ten positive confirmatory testing is sufficient to label dextromethorphan the probable culprit of this patient's hyperchloremia. The retrospective nature of this single case report, in which a single author reviewed medical records and adjudicated the contribution of DXM to each presentation, is another significant limitation in that it prevents controlling for intercurrent polysubstance use.

Although clinical bromism due to another chronic or recurrent exposure is plausible, it is a rarely encountered entity. Given the patient's clear description of dextromethorphan hydrobromide as substance of choice on innumerable occasions, and absent additional reported bromide exposures, it is unlikely that his hyperchloremia is due to another source. Notably, no other prescribed sources of exogenous bromides, such as scopolamine hydrobromide or pyridostigmine hydrobromide, are present in the patient's medical chart, nor

does evidence of exposure to other exogenous halogens exist. In addition, the patient's presentations were scattered over 10 years, and over no fewer than 16 hospitals. Finally, while we feel it is likely that the patient's chronic recurrent use of dextromethorphan with sustained concurrent rise in serum chloride concentrations is most likely to represent chronic dextromethorphan tolerance with developing dependence, this remains a proposed etiology of the findings described in this report, and undoubtedly points to the need for additional formal assessment.

Conclusion

Over a 10-year period of ED visits resulting from dextromethorphan hydrobromide use, this patient's presenting serum chloride concentrations gradually but persistently increased. This likely reflects progressively increasing serum bromide concentrations and suggests the development of physical tolerance to dextromethorphan coinciding with his consistent abuse and dose escalation. Vigilance of long-term trends in serum chloride may provide indirect evidence of tolerance in patients who chronically abuse dextromethorphan hydrobromide.

Authors' Contribution All authors participated in editing and rewriting the manuscript. SS and TO prepared the initial draft. TO prepared the statistical analysis and figure(s) and consented the patient. TO conducted all data abstraction. SB initially approached patient for consent to publish this case report and provided editorial input for the final manuscript. Jenna LeRoy provided editorial input for the final manuscript.

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Compliance with Ethical Standards

Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Conflict of Interest None.

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