Dermal Exposure to a Compounded Pain Cream Resulting in Severely Elevated Clonidine Concentration

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Abstract

Introduction Clonidine is an imidazoline derivative antihypertensive medication that is also used as adjunctive therapy for neuropathic pain disorders via topical administration. Clonidine overdose can manifest both central and peripheral alpha-adrenergic agonist effects.

Case Report A 23-year-old man presented to an emergency department with altered mental status, bradycardia, and hypertension after suspected overdose. He had rubbed a specially compounded medicinal cream over his entire body containing clonidine 0.2 % (w/w), gabapentin 6 %, imipramine 3 %, ketamine 10 %, lidocaine 2 %, and mefenamic acid 1 %. The patient presented with severe hypertension, bradycardia, and altered mental status. He was found to have a subarachnoid hemorrhage and was treated for hypertensive emergency. Toxicological analysis of initial blood samples revealed a serum clonidine concentration of 5,200 ng/ml. At 6-month follow-up, the patient had made a full recovery.

Discussion There are limited reports of topical clonidine toxicity, and to our knowledge, this case involves the highest concentration yet reported following clonidine overdose by

any route of exposure. The severely elevated serum clonidine concentration found in our patient demonstrates the possibility of toxicity resulting from inappropriate use of such a product. At high serum concentrations, the pharmacodynamic effects of clonidine appear to cause significant peripheral alpha-1 adrenergic stimulation. Toxicologists should be aware of the increasing use of topical clonidine preparations for the treatment of neuropathic pain and the potential for toxicity.

Keyword Adrenergic alpha 2 receptor agonists · Drug administration · Topical · Imidazoline receptors · Toxicology

Introduction

Clonidine is an imidazoline derivative antihypertensive medication that is also used as adjunctive therapy for neuropathic pain disorders. It is given by various routes of administration to treat pain. When administered topically, clonidine's effects on pain relief are thought to occur via modulation of peripheral alpha-2 receptors on nociceptors in the epidermis [1].

Clonidine has both central and peripheral alpha-adrenergic agonist effects. It binds central alpha-2 adrenergic receptors and modulates sympathetic outflow, resulting in decreased peripheral vascular resistance and decreased cardiac output. In overdose, clonidine is classically described as producing hypotension, bradycardia, central nervous system depression, respiratory depression, and miosis. Animal and in vitro models have demonstrated that clonidine also causes vasoconstriction, hypertension, and mydriasis via direct stimulation of peripheral alpha-1 adrenergic receptors [2]. Peripheral alpha-1 adrenergic effects associated with high-serum clonidine concentrations have previously been reported in humans following overdose [3–7].

We report a unique exposure to clonidine involving a specially compounded cream preparation resulting in an

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extremely high-serum clonidine concentration. Our case highlights the potential for toxicity from unusual clonidine formulations and provides additional evidence that clonidine pharmacodynamics at high-serum concentrations are associated with peripheral alpha-1 adrenergic effects.

Case Report

The poison center was consulted regarding a 23-year-old man, weighing 81.6 kg, who presented to an emergency department (ED) with altered mental status after suspected overdose. The patient had told his father that he rubbed an unknown amount of a prescribed, specially compounded medicinal cream “all over his body” at an unknown time. The patient had a past medical history significant for anxiety, depression, and chronic pain in his ankles after a motor vehicle accident 3 years prior. Part of his chronic pain treatment regimen included a compounded cream containing clonidine 0.2 %, gabapentin 6 %, imipramine 3 %, ketamine 10 %, lidocaine 2 %, and mefenamic acid 1 % (all weight/weight) with 1 pump dispensing 1 g out of a 120 g container. The patient typically applied 2–3 pumps topically to his feet and ankles twice a day. His other home medications included aripiprazole, clonazepam, duloxetine, oxycodone/acetaminophen, and zolpidem.

On ED presentation, the patient’s vital signs were heart rate 46 beats/min, blood pressure 180/87 mmHg, respiratory rate 21 breaths/min, temperature 95.6 F rectally, and pulse oximetry 100 % on room air. Notable findings on physical exam included decreased level of consciousness with response to painful stimuli, slurred speech, disorientation, mydriasis, and regular bradycardia. Initial workup showed normal complete metabolic profile and blood count. Acetaminophen, salicylate, and ethanol concentrations were undetectable. Electrocardiogram revealed sinus bradycardia with HR 40, QRS 104 ms, and QTc 481 ms. Urine drug screen using a competitive fluorescence immunoassay (Alere Triage® TOX Drug Screen, San Diego, CA) was presumptively positive for amphetamines, tetrahydrocannabinol, and tricyclic antidepressants. The screen was negative for methamphetamine, cocaine metabolites, phencyclidine, barbiturates, benzodiazepines, methadone, and opiates.

The patient was decontaminated using soap and water. Treatments he received while in the ED included atropine, sodium bicarbonate, and normal saline. During the ED course, his level of consciousness declined and he was intubated for airway protection. The patient was then transferred to a tertiary care hospital for further management.

On arrival to the receiving hospital, the patient remained bradycardic and severely hypertensive, his highest recorded blood pressure was 214/139 mmHg, requiring management for hypertensive crisis with hydralazine. A CT scan of the head was performed that revealed subarachnoid hemorrhage

(SAH). A subsequent cerebral CT angiogram showed no aneurysms, arteriovenous malformations, or masses.

The patient was extubated on hospital day 2. Additional history was elicited that he used dextroamphetamine/amphetamine (Adderall) at least twice in the 3 days prior to his admission; there was no history of ingestion on the day of his presentation. He was treated with corticosteroids for presumed drug-induced vasculitis. At 6-month follow-up, the patient had returned to his baseline status. Results of toxicological testing on the initial blood sample obtained upon the patient’s ED presentation are shown in Table 1. The measured serum clonidine concentration was 5,200 ng/ml (therapeutic range 0.5–4.5 ng/ml).

Discussion

Clonidine transdermal delivery (patch) systems have been available since the 1980s and pharmacokinetic studies of these products demonstrate a linear relationship between the size of the patch and the steady-state serum concentrations achieved [8]. The amount of drug administered, therefore, depends on the contact surface area of the patch rather than the size of the system reservoir. The clonidine patch systems currently available in the USA come in three sizes: 3.5, 7, and 10.5 cm². Respectively, the patches deliver a dose of 0.1, 0.2, and 0.3 mg/day; containing total clonidine contents of 2.5, 5, and 7.5 mg; and achieving mean plasma steady-state concentrations of 0.4, 0.8, and 1.1 ng/ml [9].

There is no data available specifically about the transdermal pharmacokinetics of clonidine cream preparations. Differences between patch and cream preparations, unknown absorption kinetics, and the uncertainties of our patient’s exposure preclude any meaningful calculations about the clonidine dose he may have received. By report, our patient’s cream supposedly contained 240 mg of clonidine in a full bottle; however, the cream was not available for analysis. The patient could not recall the events prior to his presentation but

Table 1 Toxicological testing of the patient’s initial serum specimen

Test	Result	Reference range
Clonidine ^a	5,200 ng/ml	0.5–4.5 ng/ml ^b
Lidocaine ^c	Not detected	1 µg/ml ^d
Monoethylglycinexylidide (MEG-X) ^c	Not detected	0.5 µg/ml ^d
Imipramine ^a	13 ng/ml	150–300 ng/ml ^b
Desipramine ^a	<10 ng/ml	150–300 ng/ml ^b

^a Measured by quantitative liquid chromatography-tandem mass spectrometry

^b Therapeutic range

^c Measured by gas chromatography

^d Reporting limit

he reportedly applied the cream to a large area of his skin. Therefore, it is conceivable that he would absorb a large amount of clonidine capable of producing the high concentration measured in his serum.

Therapeutic plasma clonidine concentrations are variably reported, but typically less than 4 ng/ml [10]. Multiple reports document toxicity resulting from dermal as well as oral exposure to clonidine patches [11, 12]. For example, a 33-year-old man who chewed and swallowed a 5-mg topical patch became obtunded and bradycardic; he was found to have a serum clonidine concentration of 9 ng/ml [13].

Several authors have reported hypertension associated with clonidine toxicity in adults and children. During an attempt to refill the subcutaneous reservoir of an intrathecal pump, a 62-year-old woman was accidentally given a subcutaneous dose of clonidine 12.25 mg and hydromorphone 48.3 mg. She developed hypertensive crisis with altered mental status attributed to possible hypertensive encephalopathy, mydriasis, seizure, and subsequent myocardial infarction [3]. In a similar case, a 51-year-old woman was given a subcutaneous dose of clonidine 18 mg and morphine 90 mg during attempted intrathecal pump reservoir refill. She subsequently developed hypertensive emergency, bradycardia, altered mental status, mydriasis, and myocardial infarction [4]. Our patient's presentation is similar to these cases demonstrating altered mental status, hypertension, and mydriasis. Unfortunately, neither of these cases reported on clonidine concentrations.

A possible mechanism to explain hypertension due to clonidine toxicity is higher serum concentrations causing more peripheral alpha-1 adrenergic effects. Domino et al. reported the case of a 28-year-old man who ingested 100 mg of clonidine and developed severe hypertension, bradycardia, and altered mental status. The patient's plasma clonidine concentration was 230 ng/ml 1 h after presentation. Serial plasma samples were obtained from the patient and a biphasic dose-response relationship was found. There was a hypertensive response when the plasma clonidine concentration was above 50 ng/ml and a hypotensive response when below 50 ng/ml [5]. In addition, at least two pediatric case reports associate clonidine concentrations above 50 ng/ml with hypertension. The combination of somnolence, bradycardia, and hypertension was reported in a 3-year-old boy with oral clonidine overdose due to an accelerated dosing error; he was found to have a serum clonidine concentration of 300 ng/ml [6]. Similarly, a 5-year-old boy with a 1,000-fold oral clonidine overdose due to a compounding error presented unresponsive, with bradycardia and hypertension, and had a serum clonidine concentration of 64 ng/ml [7]. These findings are consistent with our patient's presentation, having severe hypertension with a markedly elevated serum clonidine concentration.

Our patient's serum clonidine concentration of 5,200 ng/ml is more than 14 times greater than any we found previously reported with clonidine overdose. We performed a search of

PubMed and Embase using a combination of the terms "clonidine," "overdose," "poisoning," and "toxicity." We also searched the POISINDEX® System (Greenwood Village, CO: Thomson Healthcare) and directly contacted Boehringer Ingelheim (manufacturer of Catapres-TTS®) to inquire about any unpublished data that might be available. Lastly, we hand-searched published abstracts of the North American Congress of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists Congress from 2002 to 2012. The highest clonidine concentration our search identified was found in the Catapres-TTS® prescribing information, which cites a case involving ingestion of a clonidine powder associated with a peak plasma concentration of 370 ng/ml [9].

There are several confounded aspects to this case. First, it is unclear whether the patient may have ingested some of the cream since he did not recall the episode; however, by report, this did not occur. It is also conceivable that there was cream on the patient's skin where venipuncture was performed and this may have caused the high level we report. The complex composition of the cream introduces another source of uncertainty. Among the medications we tested for, only clonidine was present at toxic levels. Imipramine, which inhibits the reuptake of norepinephrine, was present at nontoxic levels; thus, we do not think it significantly contributed to the patient's hypertension. We did not test for mefenamic acid, gabapentin, or ketamine. Toxicity from mefenamic acid or gabapentin would not account for our patient's clinical presentation. Ketamine can cause hypertension, altered mental status, and mydriasis, and may have contributed to the patient's presentation. It was later revealed that the patient had occasionally used amphetamines; however, he did not present with a sympathomimetic toxidrome. Considering the presence of SAH in our patient, it should be noted that hypertension and bradycardia could be signs of increased intracranial pressure (the Cushing reflex). However, the Cushing reflex is classically thought to be a preterminal event associated with brainstem herniation and there was no sign of this occurring in our patient. Despite these multiple confounders, we feel that clonidine toxicity played prominent a role in the patient's presentation based on the dramatically high-serum concentration and known pharmacodynamics of clonidine. Lastly, with the cream unavailable for testing, it remains unknown whether a compounding error could have contributed to the toxicity. The Food and Drug Administration (FDA) does not regulate compounded drugs; this means that compounded drugs are not FDA-approved, and FDA does not verify their quality or safety [14]. The absence of lidocaine and its metabolite, monoethylglycinexylidide, on our testing is notable as it could suggest a compounding error during the cream preparation. Compounding of medications has been associated with significant variation from the dose intended. In one study, only 22.5 % of compounded salicylic acid solutions tested was prepared within 5 % of the prescribed dose [15].

In summary, our patient had a dramatically elevated serum clonidine concentration of 5,200 ng/ml; it was associated with the inappropriate use of a topical pain cream preparation, and higher than any previously reported toxic level. His clinical presentation of severe hypertension, altered mental status, bradycardia, and mydriasis are consistent with previously reported cases of severe clonidine overdose. Toxicologists should be aware of the increasing use of topical clonidine preparations for the treatment of neuropathic pain and the potential for toxicity.

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References

- Campbell CM, Kipnes MS, Stouch BC et al (2012) Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. *Pain* 153(9):1815–1823
- Kobinger W (1978) Central alpha-adrenergic systems as targets for hypotensive drugs. *Rev Physiol Biochem Pharmacol* 81:39–100
- Frye CB, Vance MA (2000) Hypertensive crisis and myocardial infarction following massive clonidine overdose. *Ann Pharmacother* 34(5):611–615
- Johnson ML, Visser EJ, Goucke CR (2011) Massive clonidine overdose during refill of an implanted drug delivery device for intrathecal analgesia: a review of inadvertent soft-tissue injection during implantable drug delivery device refills and its management. *Pain Med* 12(7):1032–1040
- Domino LE, Domino SE, Stockstill MS (1986) Relationship between plasma concentrations of clonidine and mean arterial pressure during an accidental clonidine overdose. *B J Clin Pharmacol* 21(1):71–74
- Farooqi M, Seifert S, Kunkel S et al (2009) Toxicity from a clonidine suspension. *J Med Toxicol* 5(3):130–133
- Romano MJ, Dinh A (2001) A 1000-fold overdose of clonidine caused by a compounding error in a 5-year-old child with attention-deficit/hyperactivity disorder. *Pediatrics* 108(2):471–472
- MacGregor TR, Matzek KM, Keirns JJ et al (1985) Pharmacokinetics of transdermally delivered clonidine. *Clin Pharmacol Ther* 38(3):278–284
- Prescribing Information (2012) Catapres-TTS(R) transdermal system, clonidine transdermal system. Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT. <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Catapres+TTS/CatapresTTS.pdf>. Accessed 24 May 2013.
- Baselt RC (2011). Clonidine. In: Disposition of toxic drugs and chemicals in Man, 9th edn, Seal Beach: Biomedical Publications. pp. 378–380.
- Harris JM (1990) Clonidine patch toxicity. *DICP* 24(12):1191–1194
- Killian CA, Roberge RJ, Krenzelok EP et al (1997) "Cloniderm" toxicity: another manifestation of clonidine overdose. *Pediatr Emerg Care* 13(5):340–341
- Raber JH, Shinar C, Finkelstein S (1993) Clonidine patch ingestion in an adult. *Ann Pharmacother* 27(6):719–722
- Food and Drug Administration (2013) Pharmacy compounding and the FDA: questions and answers. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm>. Accessed 19 Aug 2013.
- Temple TR, Nelson AA (1975) An evaluation of the quality of pharmaceutical care: a study of the pharmacist's compounding behavior. *Drug Intell Clin Pharm* 9(11):591–595