Haloperidol decanoate overdose in an adolescent

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Haloperidol is a butyrophenone antipsychotic agent available as a sustained-release (decanoate ester) parenteral formulation. Overdoses of haloperidol in oral and immediate release parenteral formulations have been associated with the production of serious cardiac conduction disturbances. We describe a case of an adolescent female who received a 5-fold overdose of haloperidol decanoate administered intramuscularly. Attenuation of the plasma concentration vs time profile produced by the sustained-release formulation appeared to coincide with the absence of serious cardiac adverse effects despite the large dose administered.

Paed Perinat Drug Ther 2006; 7: 19–22

Keywords: haloperidol – toxicity – formulation – child – pharmacokinetics

Introduction

While the experience of haloperidol overdose in paediatric patients has been previously reported[1,2], a review of the literature did not reveal information regarding overdose of sustained-release formulations of this drug in paediatric patients. Herein we report our experience of an iatrogenic overdose of haloperidol decanoate in an adolescent.

Case report

An 11 year old, 63 kg Caucasian female was admitted following an iatrogenic overdose of haloperidol decanoate, a sustained-release parenteral formulation. Her past medical history was significant for complex psychiatric illness which included post-traumatic stress disorder, dysthymic disorder, conduct disorder and self-mutilation. Her medications prior to admission included: escitalopram 20 mg daily, quetiapine 100 mg twice daily and 200 mg every evening, trozodone 300 mg every evening, naproxen 250 mg twice daily as needed, and oral contraceptives.

A decision to institute treatment with haloperidol decanoate was made and consequently, an intramuscular (IM) dose of 100 mg was prescribed. In contrast, a total 500 mg dose of haloperidol decanoate (5.0 ml total volume) was divided and administered intramuscularly (IM) in two gluteal sites. Additionally, at least two oral 5 mg doses of haloperidol were given on consecutive days after the initial medication error. At approximately 48 hours (h) after the overdose, the patient

complained of visual disturbances and fatigue. She was found to be somewhat disoriented, repeating questions to her caregivers. Subsequently, the patient was transferred to a regional hospital where the discovery of a sinus arrhythmia prompted her transfer to our institution.

Upon admission, the patient was awake, alert and oriented to person, place and time. She complained of general malaise, slight dizziness, abdominal cramps and low back pain. Vital signs revealed a temperature of 36.3 ºC, pulse (regularly irregular) of 64 beats/minute, a respiratory rate of 24 breaths per minute and a seated blood pressure of 117/61. The intake physical examination was unremarkable with no rigidity, apparent movement disorder, fever, autonomic dysfunction or neurological abnormality noted. Initial laboratory tests including a complete blood count, basic metabolic screen, renal and hepatic profile, serum creatine phosphokinase and a urinalysis were performed and were all reported to be within normal limits. An initial electrocardiogram (ECG) revealed: PR 148 msec, rate 69 beats per minute, QRS 96 msec and QT_c 407 msec. Venous access was obtained and maintenance fluids were started. In view of the potential cardiac risk associated with the haloperidol overdose, all of the patient's medications were temporarily discontinued. Dantrolene sodium and sodium bicarbonate were ordered to be immediately available as contingent treatments for neuroleptic malignant syndrome or life threatening cardiac arrhythmias.

Consequent to the perceived cardiovascular risk associated with a large haloperidol overdose, the patient was placed on a cardiorespiratory monitor and 12 lead ECGs were performed every 4 h, all of which during the first 24 h of hospitalisation displayed a sinus arrhythmia. Thereafter, the frequency of ECG evaluation was reduced to every 12 h. With the exception of hospital day 2 where the QT_c peaked at 445 msec, all other values for this and other parameters associated with the ECG (e.g. QT, QRS, PR, JT interval and morphology) were considered to be normal for age. Blood pressure, temperature and heart rate also remained within normal limits with the exception of a few, isolated episodes of bradycardia (heart rates from 42 to 64 bpm) that were noted in the night during sleep.

Neurological examination on the second day of hospitalisation revealed 2–3 beats of clonus in both lower limbs with brisk deep tendon reflexes. On the following day, the patient experienced two episodes of tremor lasting approximately 5 minutes, accompanied by the finding of clonus in the lower limbs. While there was no apparent rigidity noted on physical examination, the patient did complain of muscle stiffness. As a result of the neurological findings and complaints of muscle stiffness, benztropine treatment (1 mg twice daily) was initiated, which eliminated all abnormal neurological findings within 24 h. Escitalopram therapy was restarted on hospital day 3 as were the patient's oral contraceptives. On hospital day 4, the patient complained of nausea and difficulty in sleeping which were effectively treated with intermittent doses of ondansetron (4 mg) and a nightly dose of zolpidem (5 mg), respectively. Throughout the remaining hospital course, the patient remained asymptomatic with stable vital signs and normal ECGs. She was discharged on hospital day 14 with prescriptions for benzotropine (1 mg twice daily), escitalopram (20 mg daily), ondansetron (4 mg as needed) and oral contraceptives. Recommendations for follow-up included twice weekly ECGs, frequent assessment of vital signs (every 4 h), monitoring for extrapyramidal symptoms and neuroleptic malignant syndrome, and evaluation by psychiatry services.

Pharmacokinetics

In view of a possible relationship between plasma haloperidol concentrations and the production of severe, life-threatening adverse effects[3,4,5] and the large dose administered to the patient, total plasma haloperidol concentrations were assessed at several post-ingestion time points (Figure 1). Residual sample from daily venous blood samples obtained as a part of therapeutic phlebotomy for routine (i.e. standard of care) laboratory testing was used for this purpose (with assent of the patient and permission of the legal guardian). Serum was stored –20 ºC until analysis. The samples were shipped to National Medical Services Laboratory (Willow Grove, PA) for haloperidol assay using a modification of validated gas chromatography methods[6,7]. The assay had a lower limit of quantitation of

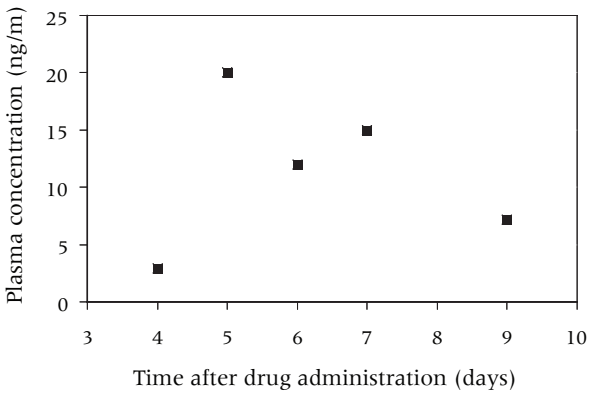

Figure 1 Serum concentration vs time plot of haloperidol following a single intramuscular dose of haloperidol decanoate. Time is denoted as days after drug administration.

0.5 ng/ml and an intra- and inter-run imprecision of < 10% and < 20%, respectively.

The post-dose serum haloperidol concentration vs time data is illustrated in Figure 1. Consequent to the possibility of on-going absorption at six to seven days after IM administration of the sustained release haloperidol formulation (as suggested by shape of the plasma concentration vs time profile), the final two concentrations were used to estimate the apparent elimination rate constant (Ke) and elimination half life ($t_{½}$ = 0.693/Ke); the later yielding a value of 50.5 h.

Discussion

Haloperidol is a butyrophenone antipsychotic agent used for the treatment of a variety of disease states such as conduct disorders in children with symptoms of impulsivity, difficulty in sustaining attention, aggressive behaviour, mood lability, and poor frustration tolerance[8]. The drug is extensively bound to tissue and plasma protein (average = 92 %), having an apparent volume of distribution of 18–30 l/kg. It is extensively metabolised to inactive compounds, largely by the polymorphically expressed enzyme CYP2D6[8,9].

Haloperidol is available in several formulations including immediate release oral and intramuscular preparations as well as a sustained release intramuscular product, haloperidol decanoate. Time to peak concentration (t_{max}) is approximately 2–6 h, 20 minutes and 6 days, respectively, for these formulations[3,9]. As a function of the sustained-release properties of the decanoate ester, the apparent elimination half life ($t_{½}$) for haloperidol from this formulation may be up to 3 weeks which is in contrast to a $t_{½}$ of approximately 21 h for the immediate release formulations[3,9,10]. As a result of the long apparent $t_{½}$ for the deaconate formulation, the time to reach steady state is approximately 3 months after the initiation of therapy[10].

As illustrated by the haloperidol concentrations in our patient, apparent peak plasma haloperidol concentrations were not attained until approximately 5–7 days following administration of the single IM dose. The unexpectedly short elimination $t_{½}$ of approximately 50 h may be due to the limited number of samples available to accurately determine the true terminal elimination rate constant.

The pharmacological and toxicological effects of haloperidol include modulation of dopamine in the central nervous system, alpha receptor blockade and direct effects on cardiac sodium and potassium channels[11,12]. The cardiac effects are similar to those associated with Class III antiarrhythmic agents which include reduced AV nodal conduction and associated wide complex arrhythmias. Prolongation of QT_c as an antecedent event for Torsades de pointes and sudden death can occur at normal therapeutic doses or in overdose[4,5,11,13]. In cases of experimental haloperidol overdose in an animal (guinea pig) model, increases in the myocardium to plasma concentration ratio to values > 4 have been associated with an increased risk of serious cardiac arrhythmias and sudden death[4].

In view of the potential cardiac risk associated with haloperidol overdose in adults with ingestions ranging from 300 to 1000 mg[14,15], intensive monitoring was initiated in the patient described herein. Our patient did not experience cardiovascular signs or symptoms expected to be associated with haloperidol overdose (e.g. hypotension, hyperthermia, persistent increase in QT_c, protracted bradycardia)[4,5,11,13] with the possible exception of isolated episodes of mild bradycardia. Multiple ECG assessments revealed a maximal QT_c of 445 msec, a value that was not associated with a significant cardiac arrhythmia.

In contrast to the relative absence of cardiovascular effects in our patient, she did experience neurological findings (e.g. brisk deep tendon reflexes, clonus, apparent muscle rigidity) associated with haloperidol administration. Extrapyramidal symptoms (EPS) are commonly seen with haloperidol overdose and may occur in up to 25% of patients receiving therapeutic doses[16]. Some studies have found the decanoate formulation to be associated with a much higher incidence of adverse reactions, particularly EPS, as compared to oral formulations[3]. Benztropine is generally considered to represent a treatment of choice for EPS associated with phenothiazine or butyrophenone treatment and in our patient, resulted in complete resolution of symptoms.

In a recent study of 12 subjects with schizophrenia who received a single IM haloperidol dose of 7.5 mg, peak plasma concentrations ranged from approximately 1.0 to 21 ng/ml (mean 9.4 ± 5.3 ng/ml) and the post-dose QT_c increased by a mean value of 4.2 msec[17]. No subject had a QT_c greater than 441 msec and no clinically significant cardiac events occurred. In this study, approximately, 33% of patients required anticholingeric medication for the treatment of EPS[17]. These observations are not dissimilar to those observed in our patient despite her receiving a haloperidol dose that was approximately 67-fold greater than the one used in the aforementioned study. The apparent peak haloperidol serum concentration in our patient was similar to

the maximal values reported by Harvey et al.[17]. Thus, it would appear that the sustained-release properties of the decanoate formulation were sufficient to attenuate the expected (i.e. based upon the total dose injected) serum haloperidol concentrations and as a result, the production of serious cardiac and/or neurological toxicity.

Conclusions

This case illustrates that the toxicity profile from a large dose of haloperidol decanoate may be quite different from that following comparable or lower doses of oral or parenteral haloperidol lactate, thus demonstrating the importance of considering formulation in the evaluation of haloperidol overdose.

Acknowledgement

The authors gratefully acknowledge the contributions made by Ralph E. Kauffman, M.D. in the discussion and management of this patient.

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PPDT 0145, *Accepted for publication:* 21 December 2005
Published Online: 14 March 2006
doi:10.1185/146300905X75325