

A CASE REPORT OF AN ULTRA-RAPID METABOLIZER ON DEPOT FORMULATIONS OF RISPERIDONE AND HALOPERIDOL AND REFLECTIONS ON METABOLIC PATHWAYS

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Polycyclic aromatic hydrocarbons (PAH) in tobacco are potent inducers of Cytochrome P450 (CYP) 1A2, which metabolizes a plenty of drugs including antipsychotics such as olanzapine or clozapine. With regard to haloperidol and risperidone, CYP3A4 is supposed to be the major isoenzyme. We present the case of a 60-year old woman who suffered from chronic schizophrenia and smoked more than 40 cigarettes per day, which indicates that PAH also induces CYP3A4, causing ultrarapid metabolism of risperidone and haloperidol with subtherapeutic drug levels both after oral or intramuscular depot administration. *Acta Medica Medianae 2014;53(3):42-45.*

Key words: risperidone, haloperidol, ultra-rapid metabolism, tobacco, CYP3A4, schizophrenia

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Introduction

The treatment of chronic schizophrenia with prominent negative symptoms poses a formidable challenge for both patients and psychiatrists as well as their relatives (1-3). Residual syndrome occurs in varying degrees of severity in about 30% of the patients. However, negative and positive symptoms may be found simultaneously and thus complicate psychopathology. Sometimes, they are called the mixed type of residuum. In general, atypical antipsychotics together with psychological and social approaches are reasonable. However, a lack of compliance with regard to long-term pharmacological treatment can deteriorate the prognosis. In order to improve therapeutic adherence depot formulations such as haloperidol, decanoate or more recently Risperdal consta® have been developed. Although depot formulations are injected with intervals of two to four weeks, they do not warrant therapeutic serum levels in fast metabolisers, due to either enzyme induction or polymorphisms. We present a case of a heavy female smoker suffering from chronic schizophrenia who did not generate adequate serum levels of haloperidol or risperidone even after the application of high dose depot formulations.

Case report

A woman suffering for more than 20 years from chronic schizophrenia (ICD 10 F20.5) was referred to the Department of Psychiatry due to supposed antipsychotic overdose. Her husband reported an increasing mutism and a low level of activity starting a few days before. On admission she was moving like a robot with occasionally bizarre movements and appeared extremely mistrustful, so that psychiatric assessment was very limited. She denied suicidal ideas and initially accepted medical treatment. She was a heavy smoker (>40 cigarettes per day) and had a history of hyperthyreosis. Physical examination including ECG did not reveal clinically relevant general or neurological findings.

She had been treated with risperidone (Risperdal consta®) up to 75 mg i.m. every two weeks and haloperidol decanoate 100 mg every 3 weeks obviously due to a prior lack of adherence. Clinical laboratory (blood count, liver and renal panel, blood clotting panel, electrolytes, C-reactive protein, TSH) did not show substantial pathological results apart from low TSH (0.19 mU/l). Unexpectedly, haloperidol serum levels were very low (4.7 µg/l NR: 3-25 µg/l) and both risperidone (4.9 ng/ml NR: 20-60 ng/ml) and 9-OH-risperidone (10.3 ng/ml NR: 20-60 ng/ml) serum levels were markedly below the normal range. Drug levels were measured using a standard LC/MSMS-method (4).

Initially, we administered biperidene without much success, as catatonia and drug-induced extrapyramidal disorder could not be clearly delineated. After a discussion with the patient and her husband (attorney) we suggested a compassionate use of increased haloperidol decanoate (up to 200 mg every 2 weeks) and

clozapine (up to 50 mg tid). The rationale for this approach was that the disorder had not responded to various monotherapies for years, that she strictly refused alternatives such as ECT and thus developed EP symptoms following typical antipsychotics (5). Hyperthyreosis was treated with methimazol, and transiently oral haloperidol, lorazepam and pantoprazole were applied. The patient improved gradually and could be discharged after 8 weeks. At this time haloperidol levels were up to 15 µ/ml, being within the therapeutic window.

Within a week's time she was again admitted to the emergency department due to loss of appetite, energy, loss of activities and affective flattening. She presented with a catatonic stuporous syndrome including incoherent thoughts. After emergency assessment she was referred to the Department of Psychiatry. The following serum levels were determined: haloperidol 7.7 µg/l, clozapine <0.05 mg/l (NR: 0.05-0.7 mg/l) and desmethyl-clozapine <0.05 mg/l (NR: 2-0.7 mg/l). Haloperidol levels were controlled a week later, being 4.2 µg/l. Apparently, the patient had been noncompliant with regard to oral clozapine (50 mg tid) and the remaining oral haloperidol dose (2mg bid) in addition to a supposed ultrarapid metabolism of haloperidol (200 mg haloperidol decanoate every 2 weeks).

We again discussed possible approaches with the family, attorney and patient. Then, we decided to replace haloperidol by flupenthixol decanoate (40 mg every 2 weeks). Moreover, we gradually increased the dose of clozapine (100-50-100 mg). She remarkably improved within 6 weeks and was able to run with her household. A few weeks later we unfortunately had to

discontinue clozapine due to noncompliance and continued monotherapy with flupenthixol decanoate. Fortunately, her flupenthixol serum levels within the lower normal range. She could be discharged in a sufficient state of health and referred to an outpatient clinic without re-admission for at least one year. The authors thank the patient and her attorney (husband) for giving us their written informed consent for evaluation and publishing the case.

Metabolism of risperidone and haloperidol

The schematic metabolic pathways of risperidone are given in Figure 1. The major active metabolite is 9-OH-risperidone, hydroxylation involving Cytochrome P450 (CYP) 2D6 (6-8). CYP3A4 catalyzes degradation to inactive acidic metabolites of both risperidone and his active metabolite. 9-OH-risperidone has been meanwhile marketed as an antipsychotic itself (InvegaR, XepionR). Obviously, CYP3A4 plays a decisive role with regard to risperidone metabolism (9,10).

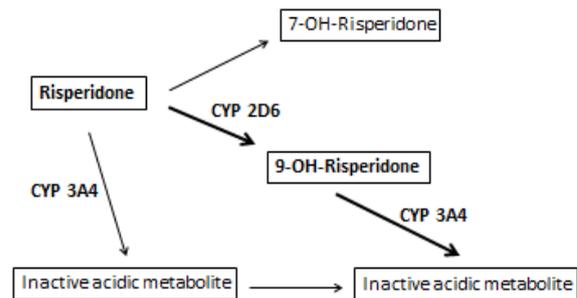


Figure 1: Outline of metabolic pathways of risperidone

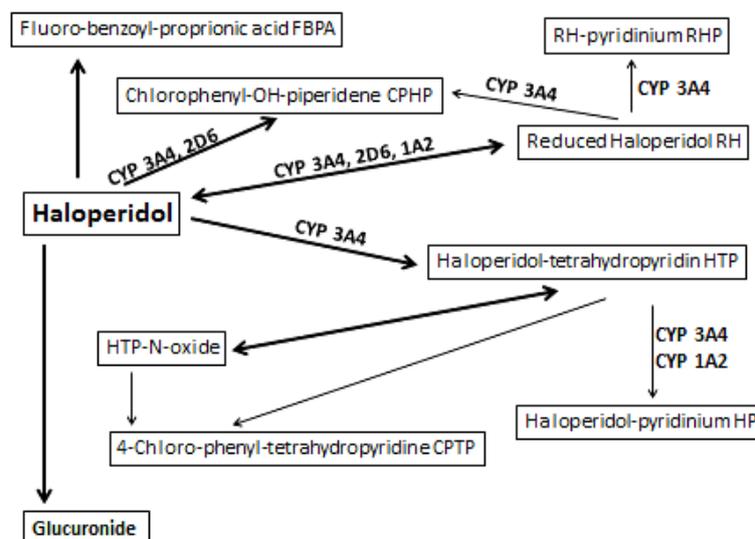


Figure 2: Outline of major metabolic pathways of haloperidol

CPHP: 4-(4-chlorophenyl)-4-hydroxypiperidene

FBPA: p-fluorobenzoyl-propionic acid

HP(+): 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxybutyl]-pyridinium

HTP: 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxybutyl]-1,2,3,6-tetrahydropyridine

RHP reduced haloperidol: 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-hydroxybutyl]-4-piperidinol

RHP(+): 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-hydroxybutyl]-pyridinium

The metabolism of haloperidol is much more complicated and a simplified scheme is given in Figure 2. The pathways have been depicted according to various published data (11-13), and chemical terms have been abbreviated for better understanding. Pyridinium metabolites play a major role and are supposed to have MPP+[1-methyl-4-phenylpyridinium]-like neurotoxic properties. First, haloperidol is metabolized to a tetrahydropyridine derivative (HTP) and reduced to RHP (reduced haloperidol), the latter being the major active metabolite of haloperidol (14,15). These compounds lead then to pyridinium derivatives (HP+, RHP+). Apart from some additional pathways, e. g. formation of N-oxides, glucuronidation may be an important step to finally eliminate haloperidol (16). It is not the aim of this paper to go into details but to notice that CYP3A4 and to lesser extent CYP2D6, CYP1A2 and other CYP enzymes are involved in the metabolism of haloperidol. Moreover, particularly induction of CYP3A4 facilitates the generation of pyridinium derivatives, which may increase toxicity of haloperidol. Although CYP1A2 is more prone to be induced by tobacco smoke (17,18), polycyclic hydrocarbons do also activate CYP3A4 gene transcription and are therefore likely to induce the enzyme in clinical terms (19).

Discussion

Drug interactions with antipsychotics due to enzyme induction or inhibition are important issues of clinical practice (20-23). It is certainly wise to use drug monitoring techniques and to regularly consult respective data bases. With regard to heavy smokers we know that particularly polycyclic aromatic hydrocarbons (PAH) induce

CYP1A2 and therefore accelerate elimination of many drugs (18). Clozapine or olanzapine are important examples with clinically relevant interactions with tobacco smoke which require dose adjustment.

However, drugs metabolized mainly via CYP3A4 may be also concerned (24). The aforementioned case report of 60-year old heavy smoker suffering from schizophrenia shows that haloperidol, which is metabolized by both CYP3A4 and CYP1A2, and notably risperidone, which is metabolized almost exclusively by CYP3A4, can be seriously affected. Rapid metabolism of both risperidone and haloperidol based on CYP2D6 genotypes has been already published following oral administration of the drugs (25,26). The new findings in this paper are that Cytochrome P460 isoenzyme 3A4 may be probably induced by heavy tobacco abuse, which may lead to ultrarapid metabolism and subsequently to subtherapeutic drug levels of both haloperidol and risperidone no matter what way of administration had been chosen. Moreover, this rapid metabolism was almost complete with regard to risperidone even after intramuscular depot injection.

Conclusion

Ultrarapid metabolism after intramuscular depot injections of haloperidol and risperidone was observed in a woman suffering from chronic schizophrenia who smoked more than 40 cigarettes per day. With regard to risperidone, the metabolism was almost complete. Fortunately, the patient developed sufficient serum levels following flupenthixol decanoate injections, as oral administration of drugs was no alternative due to incompliance.

References

1. Semple D, Smyth R. Oxford handbook of Psychiatry. Oxford: Oxford University Press; 2009:169-22. [[CrossRef](#)]
2. Haro JM, Novick D, Bertsch J, Karagianis J, Dossenbach M, Jones PB. Cross-national clinical and functional remission rates: Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) study. *Br J Psychiatry* 2011; 199(3):194-201. [[CrossRef](#)] [[PubMed](#)]
3. Nickl-Jockschat T, Schneider F. Schizophrenie, schizotyp und wahnhaftige Störungen (F2). In: Schneider F, hrsg. *Facharztwissen Psychiatrie und Psychotherapie*. Heidelberg: Springer Verlag; 2012:259-93. German. [[CrossRef](#)]
4. Ferner I, Thurman E. *Liquid chromatography-Time of Flight Mass Spectrometry: Principles, Tools and Applications for Accurate Mass Analysis*. New York: Wiley; 2009.
5. Bains JJS, Nielsens. Combining depot antipsychotic medication with novel antipsychotics in forensic patients: a practice in search of a principle. *Psychiatric Bulletin* 2003; 27:14-6. [[CrossRef](#)]
6. Mannens G, Huang ML, Meudermans W, Hendrickx J, Woestenborghs R, Heykants J. Absorption, metabolism and excretion of risperidone in humans. *Drug Metab Dispos* 1993; 21(6):1134-40. [[PubMed](#)]
7. Fang J, Bourin M, Baker GB. Metabolism of risperidone to 9-hydroxy-risperidone by human cytochrome P450 2D6 and 3A4. *Naunyn Schmiedebergs Arch Pharmacol* 1999; 359(2):147-51. [[CrossRef](#)] [[PubMed](#)]
8. Berecz R, Dorado P, De La Rubia A, Cáceres MC, Degrell I, Llerena A. The role of cytochrome P450 enzymes in the metabolism of risperidone and its clinical relevance for drug interactions. *Curr Drug Targets* 2004; 5(6):573-9. [[CrossRef](#)] [[PubMed](#)]
9. Odou P, Levron J, Luyckx M, Brunet C, Hugues R. Risperidone drug monitoring: a useful tool? *Clinical Drug Investigation* 2000; 19(4):283-92. [[CrossRef](#)]
10. Borison RL. Risperidone: pharmacokinetics. *J Clin Psychiatry Monogr* 1994; 14: 253-5.
11. Avent KM, DeVoss. P450-mediated metabolism of haloperidol and reduced haloperidol to pyridinium

- metabolites. *Chem Res Toxicol* 2006; 19:914-20. [[CrossRef](#)][[PubMed](#)]
12. Fang J, Baker GB, Silverstone PH, Coutts RT. Involvement of CYP3A4 and CYP2D6 in the metabolism of haloperidol. *Cell Mol Neurobiol* 1997; 17(2):227-33. [[CrossRef](#)][[PubMed](#)]
 13. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. *Clin Pharmacokinet* 1999; 37: 435-56. [[CrossRef](#)][[PubMed](#)]
 14. Desai M, Tanus-Santos JE, Li L, Gorski JC, Arefayene M, Liu Y, et al. Pharmacokinetics and QT interval pharmacodynamics of oral haloperidol in poor and extensive metabolizers of CYP2D6. *Pharmacogenomics J* 2003;3(2):105-13. [[CrossRef](#)][[PubMed](#)]
 15. Kang HJ, Lee SS, Lee CH, Shim JC, Shin HJ, Liu KH, et al. Neurotoxic pyridinium metabolites of haloperidol are substrates of human organic cation transporters. *Drug Metab Dispos* 2006;34(7):1145-51. [[CrossRef](#)][[PubMed](#)]
 16. Johansson T, Weidolf L, Popp F, Tacke R, Jurva U. In vitro metabolism of haloperidol and sila-haloperidol: new metabolic pathways resulting from carbon/silicon exchange. *Drug Metab Dispos* 2010; 38(1): 73-83. [[CrossRef](#)][[PubMed](#)]
 17. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet* 1999; 36: 425-438. [[CrossRef](#)][[PubMed](#)]
 18. Fankhauser MP. Drug interactions with tobacco smoke: Implications for patient care. *Current Psychiatry* 2013; 12(1):12-6.
 19. Kumagai T, Suzuki H, Sasaki T, Sakaguchi S, Miyairi S, Yamazoe Y, et al. Polycyclic aromatic hydrocarbons activate CYP3A4 gene transcription through human pregnane X receptor. *Drug Metab Pharmacokinet* 2012; 27(2): 200-6. [[CrossRef](#)][[PubMed](#)]
 20. Ereshefsky L. Pharmacokinetics and drug interactions: update for new antipsychotics. *J Clin Psychiatry* 1996;57 Suppl 11: 12-25. [[PubMed](#)]
 21. Sharif ZA. Pharmacokinetics, metabolism, and drug-drug interactions of atypical antipsychotics in special populations. *J Clin Psychiatry* 2003; 5(Suppl 6):22-5.
 22. Bleakley S. Identifying and reducing the risk of antipsychotic drug interactions. *Progr Neurol Psychiatr* 2012; 3-4: 20-4. [[CrossRef](#)]
 23. Hiemke C, Pfuhlmann B. Interactions and monitoring of antipsychotic drugs. *Handb Exp Pharmacol* 2012;(212):241-65. [[CrossRef](#)][[PubMed](#)]
 24. Gardiner SJ, Begg EJ. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. *Pharmacol Rev* 2006;58(3):521-90. [[CrossRef](#)][[PubMed](#)]
 25. Scordo MG, Spina E, Facciola G, Avenoso A, Johansson I, Dahl ML. Cytochrome P450 2D6 genotype and steady state plasma levels of risperidone and 9-hydroxyrisperidone. *Psychopharmacology (Berl)* 1999;147:300-5. [[CrossRef](#)][[PubMed](#)]
 26. Gassó P, Papagianni K, Mas S, de Bobadilla RF, Arnaiz JA, Bernardo M, et al. Relationship between CYP2D6 genotype and haloperidol pharmacokinetics and extrapyramidal symptoms in healthy volunteers. *Pharmacogenomics* 2013;14:1551-63. [[CrossRef](#)][[PubMed](#)]

PRIKAZ BOLESNIKA SA ULTRA BRZIM METABOLIZMOM DEPO FORMULACIJA RISPERIDONA I HALOPERIDOLA I ANALIZA MOGUĆIH MEHANIZAMA

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Policiklični aromatični ugljovodonici (PAU) u duvanu mogu lako da indukuju citohrom P450 (CYP) 1A2, koji metaboliše veliki broj lekova, uključujući i antipsihotike poput olanzepina ili klozapina. U poređenju sa haloperidolom i risperidonom, CYP3A4 smatra se glavnim izoenzimom. Predstavljamo slučaj šezdesetogodišnje žene koja je bolovala od hronične šizofrenije i koja je pušila više od 40 cigareta dnevno, što ukazuje da PAU takođe indukuje CYP3A4, što dalje izaziva ultra brzu metabolizaciju risperidona i haloperidola sa subterapijskim nivoima lekova, kako nakon oralne tako i nakon intramuskularne depo administracije. *Acta Medica Medianae* 2014;53(3):42-45.

Ključne reči: risperidon, haloperidol, ultra brza metabolizacija, duvan, CYP3A4, šizofrenija