# REVERSIBLE METABOLISM OF DRUGS

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CONTENTS

| | |
|---|---|
| Summary | 2 |
| Introduction | 2 |
| General models of reversible metabolism | 3 |
| *Calculations of drug and metabolite parameters* | 3 |
| *Linear and non-linear variations* | 6 |
| Metabolic pathways of haloperidol | 8 |
| Pharmacological properties of reduced haloperidol | 10 |
| Pharmacokinetics and pharmacodynamics of haloperidol and reduced haloperidol | 12 |
| *Guinea-pig studies* | 12 |
| *Human studies* | 12 |
| Clinical implications | 18 |
| Conclusions | 21 |
| References | 21 |

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## SUMMARY

Many drugs undergo reversible metabolism. The basis of our understanding of this process is the reversible metabolism of prednisone (PD) - prednisolone (PL). The pharmacokinetics of reversible metabolism requires the use of four area under the curve values integrated into four equations for clearance (CL). Other variables, such as linear versus non-linear disposition, can play important roles in reversible metabolism. Of recent interest is the reversible metabolism of haloperidol which consists of an interconversion process between the parent drug haloperidol (HL) and its reduced metabolite (RH). However, the interconversion of HL-RH differs from the PD-PL model in that, whereas PD and PL are both active, RH is considered to be a therapeutically inactive, possibly toxic, metabolite. This article reviews the pharmacodynamic and pharmacokinetic properties of HL and RH and the possible clinical effects that can result from this reversible metabolism.


## INTRODUCTION

The disposition of drugs that undergo a reversible metabolic process is under-appreciated. It has been well established that compounds such as dapsone, sulindac, sulfonamides and steroids have metabolites that can revert back in part to their parent drug /1-4/. Recently, antipsychotic drugs, such as chlorpromazine and haloperidol, were also reported to undergo a reversible metabolic process /5,6/. Haloperidol (HL) is metabolized to reduced haloperidol (RH) which is reoxidized back to HL. Numerous other agents could possess this ability to be converted back to their parent form but this metabolic process can easily be overlooked due to the absence of studies in which metabolites are administered directly to animals or humans, or to metabolite instability in body fluids. Furthermore, differences in animal species could contribute to the difficulty of

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Abbreviations:
HL = Haloperidol, RH = Reduced haloperidol, PD = prednisone, PL = Prednisolone, CL = Clearance, Cp = Plasma Concentration, D = Dose, $V_{max}$ = Maximum rate of conversion, $K_m$ = Concentration of drug/metabolite at half the value of $V_{max}$, $AUC_m^p$ = Area under the curve for the metabolite when parent drug is administered, $AUC_p^m$ = Area under the curve for the parent drug when the metabolite is administered

identifying reversible metabolic pathways. For example, reversible metabolism of haloperidol is present in guinea-pigs but not in rats. Rats only convert reduced haloperidol to HL.

Mathematical models describing reversible metabolism are complex; moreover, when alterations occur in these fundamental parameters, results can be difficult to predict. Another complicating factor is that reversible metabolism adds an extra "dimension" to the traditional concepts of clearance, volume of distribution, residence time and other parameters determined by classical kinetic calculations. The major contributions towards understanding this complex relationship have been from investigations of the prednisolone (PL) - prednisone (PD) model /7/. Although mathematical relationships were developed by investigating prednisolone and prednisone, their clinical application has not been fully examined.

This article examines and expands the information regarding reversible metabolism by considering haloperidol and reduced haloperidol as a model for basic and clinical investigations. Haloperidol is a commonly prescribed medication used to treat a variety of psychiatric and medical disorders.

## GENERAL MODELS OF REVERSIBLE METABOLISM

A general model of reversible metabolism is presented in Figure 1. This model assumes that both drug and metabolite have a linear disposition and that elimination occurs only through their central compartments. Both compounds could have a distribution to their respective tissue compartments. The tissue compartment could also represent drug receptor sites. The other assumption made is that this basic model follows the laws of mass action in which the drug and metabolite plasma concentrations are in equilibrium with the tissue compartments or receptor sites.

### Calculations of drug and metabolite parameters

The determination of clearances from Figure 1 has been previously published /7/ and forms the basis of interpreting the kinetic aspects of reversible metabolic systems. The elimination is determined by four clearances (CL). $CL_{1\,0}$ and $CL_{2,0}$ represent the total elimination

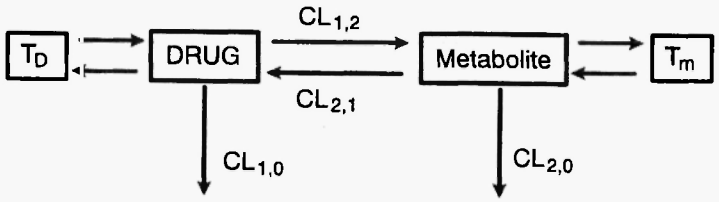


**Fig. 1:** General model of reversible metabolism (adapted from /7/).
$T_D$ = Tissue concentration of the parent drug; $T_m$ = Tissue concentration of metabolite; CL = Clearance; $CL_{1\,0}$ = Parent drug clearance; $CL_{2\,0}$ = Metabolite clearance; $CL_{1\,2}$ = Conversion CL of parent drug; $CL_{2,1}$ = Conversion CL of metabolite.

clearances for the central compartment for the parent drug and metabolite, respectively. $CL_{1,2}$ denotes the conversion clearance from the parent drug to the metabolite. $CL_{2\,1}$ is the conversion clearance of the metabolite to the parent drug.

Differing from classical pharmacokinetic methods, reversible metabolism clearance determinations require the assessment of four area under the curve (AUC) values from administration of both parent drug and metabolite at the same dosages (D). $AUC^{p}_{m}$ is defined as the area under the curve of the metabolite (subscript) when the parent drug is administered (superscript). $D_m$ represents the metabolite dose and $D_p$ is the parent drug dose administered. The following four equations can be solved to yield the CL determinations shown in Figure 1:

$$CL_{1,0} = \frac{D_p\, AUC^{m}_{m} - D_m\, AUC^{p}_{m}}{AUC^{p}_{p}\, AUC^{m}_{m} - AUC^{p}_{m}\, AUC^{m}_{p}}$$

$$CL_{2,0} = \frac{D_m\, AUC^{p}_{m} - D_p\, AUC^{m}_{p}}{AUC^{p}_{p}\, AUC^{m}_{m} - AUC^{p}_{m}\, AUC^{m}_{p}}$$

$$CL_{1,2} = \frac{D_m\, AUC^{p}_{m}}{AUC^{p}_{p}\, AUC^{m}_{m} - AUC^{p}_{m}\, AUC^{m}_{p}}$$

$$CL_{2,1} = \frac{D_p\, AUC^m_p}{AUC^p_p\, AUC^m_m - AUC^p_m\, AUC^m_p}$$

Thus, the total CL for the parent drug is $CL_{1.0} + CL_{1,2}$ and the total CL for the metabolite is $CL_{2.0} + CL_{2.1}$.

The terms of $E_{1.2}$ and $E_{2,1}$ can be seen as the efficiencies of $CL_{1,2}$ and $CL_{1.2}$, respectively, where these values represent the probability of the drug or metabolite not being converted back to its original form /7/. These values can be determined by $CL_{2.1}$ and $CL_{2.0}$ where

$$E_{1,2} = CL_{2,0} / (CL_{2,1} + CL_{2,0}) \text{ and}$$

$$E_{2.1} = CL_{1.0} / (CL_{1.2} + CL_{1.0}).$$

The values $Kd^p_m$ and $Kd^m_p$ represent interconversion coefficients which are rate functions of the system's CLs and can be calculated by

$$Kd^p_m = CL_{1,2} + CL_{2,1} / (CL_{2,1} + CL_{2,0})^2 \text{ and}$$

$$Kd^m_p = CL_{1.2} + CL_{2,1} / (CL_{1.2} + CL_{1,0})^2.$$

RHO values are used to characterize reversible systems and represent the fraction of the dose transferred to the metabolite for the first time and vice versa. Therefore,

$$RHO^p_m = CL_{1.2} / (CL_{1.2} + CL_{1.0}) \text{ and}$$

$$RHO^m_p = CL_{2.1} / (CL_{2.1} + CL_{2,0}).$$

Exposure enhancement ratio (EE) represents the degree of parent drug exposure in the presence and absence of back conversion:

$$EE = 1 + \frac{CL_{1.2}\, CL_{2.1}}{CL_{1.0} + CL_{2.1} + CL_{1.2} + CL_{2.0}}$$

EE will always be greater than unity and serves to conserve the drug.

When the drug and metabolite can be administered intravenously, other parameters of reversible metabolism can be determined such as volume of distribution, mean residence time (defined as the duration

of time a drug spends in the body or organ before being eliminated irreversibly) and sojourn time (defined as the average length of time a drug remains in the system prior to its metabolism or elimination).

The determination of volume of distribution ($V_{dss}$) at steady state for both the parent drug and its metabolite can be calculated utilizing the dose administered and the AUCs. However, an additional variable requires inclusion - the AUMC. The AUMC is defined as the first moment of the plasma concentration-time profile /7/. This moment is determined by the same method as in calculating AUC after multiplying all plasma concentrations by their respective time values. $V_{dssp}$ (parent drug) and $V_{dssm}$ (metabolite) can be determined by the following equations:

$$V_{dssp} = Dose^{p} \frac{(AUC_{m}^{m})^2 * AUMC_{p}^{p} - AUC_{m}^{p} * AUC_{p}^{m} * AUMC_{m}^{m}}{(AUC_{p}^{p})^2 * (AUC_{m}^{m})^2 - (AUC_{m}^{p} * AUC_{p}^{m})^2}$$

$$V_{dssm} = Dose^{m} \frac{(AUC_{p}^{p})^2 * AUMC_{m}^{m} - AUC_{p}^{m} * AUC_{m}^{p} * AUMC_{p}^{p}}{(AUC_{m}^{m})^2 * (AUC_{p}^{p})^2 - (AUC_{p}^{m} * AUC_{m}^{p})^2}$$

The difference between mean residence time and sojourn time is that alterations in clearances or volumes of the metabolite can change residence time of the parent drug and vice versa. Sojourn time is only dependent upon the clearance or volume of the same compound (metabolite or parent drug) /7/. These additional pharmacokinetic parameters are usually determined in animal models since it is not possible to administer metabolites intravenously to humans subjects for ethical reasons.

**Linear and non-linear variations**

The basic model for reversible metabolism is represented in Figure 1. Two variations have been reported where elimination of either the parent drug ($CL_{1,0}$) or metabolite ($CL_{2,0}$) from the central department does not occur. Calculations for CLs have been modified to reflect these variations /8/.

Non-linear disposition can also occur in reversible metabolic systems. The interconversion between PL and PD was reported to be dose-dependent and non-linear in man and dogs /9,10/. Data from PL

and PD plasma concentrations at steady-state were fitted to the Michaelis-Menten equation:

$$PD = \frac{V_{max}(PD) \cdot PL}{K_m + PL}$$

The total PD concentration was shown to be highly correlated to the total PL concentration ($r^2$ = -0.938). The Michaelis-Menten parameters had calculated values of $V_{max}(PD)$ = 26.9 ng/ml and $K_m$ = 658 ng/ml /11/. These values represent PD and PL parameters and as a result population parameters can be established similar to phenytoin pharmacokinetics.

One major variation includes non-linear elimination of drug or metabolite not from the central compartment (either $CL_{1.0}$ or $CL_{2.0}$). However, non-linear disposition ($V_{max}$ and $K_m$) could possibly result at $CL_{2,1}$ /11/. Most compounds do not exhibit these particular patterns as elimination usually occurs from the central compartment.

The non-linear aspect of PL and PD interconversion has been extensively examined in the rat model with drug elimination from the central and peripheral compartments /12/. Using the basic model shown in Figure 1, non-linear disposition could theoretically affect various combinations of CLs. In fact, through enzymatic processes, fifteen different combinations of clearance could take place. For example, non-linear metabolism in $CL_{1.0}$ and $CL_{12}$ could be found. Each CL could theoretically have different $V_{max}$ and $K_m$ values. PD and PL were administered at doses of 5, 10, 25 and 50 mg/kg to rats and the four CL parameters were calculated. From these different doses, no statistically significant changes in the mean $CL_{1.0}$ (69.7-79.5 ml/min/kg, respectively) and mean $CL_{21}$ (33.5-53.1 ml/min/kg, respectively) were found. Yet a significant decrease in $CL_{2.0}$ from 129.0 ml/min/kg to 2.6 ml/min/kg and $CL_{12}$ from 5.0 ml/min/kg to 1.2 ml/min/kg were observed. These results suggest that at least two saturable elimination pathways exist at these dosages in the prednisone-prednisolone reversible metabolic process. Interestingly, the recycled fraction (R)F values increased from 0.011 (5 mg/kg) to 0.016 (50 mg/kg). Below doses of 2 mg/kg, the kinetics of PD and PL are linear as reversible metabolism is minimal.

As for PL and PD, HL and RH could exhibit non-linear reversible disposition. In over 100 psychiatric patients treated with haloperidol,

steady-state HL and RH plasma concentrations were measured /13/. At HL plasma levels greater than 30 ng/ml, large increases in RH were observed, suggesting a non-linear relationship. This relationship of RH to HL was similar to the plot of PL versus PD /10/. The possible pathways for saturable metabolism of HL and RH remain to be determined.

## METABOLIC PATHWAYS OF HALOPERIDOL

The metabolism of haloperidol varies among the different animal species and humans. In both animal models and humans, haloperidol metabolism involves oxidative dealkylation at the C-N bond of the central butyrophenone chain to form 4-fluorobenzoylpropionic acid and piperidine metabolites, as shown in Figure 2 /14,15/. Other metabolic routes are formation of an aliphatic alcohol via reduction (RH) and aromatic hydroxylation.

The guinea-pig model /16/ closely resembles human disposition of haloperidol. In comparison of guinea-pig and rat hepatic microsomal preparations, rats could not form RH from HL but could oxidize RH back to HL /16/. In guinea-pigs, RH concentrations were observed after HL administration and HL concentrations were observed after RH administration. The formation of RH was shown to be rapid and to occur within 1 hour after HL administration /17/. Since HL and RH were measured in very low concentrations in the urine, these compounds require conversion to more polar conjugates prior to excretion.

In man, three conjugated metabolites of HL and RH were determined in urine by HPLC and immunological detection using three types of anti-HL antisera /18/. The main urinary metabolite detected after 24 hours was HL-glucuronide which accounted for 18% of the total dose administered. For RH, other metabolites included RH glucuronide and RH sulfate, and both were found to be less than 1% in man. Other metabolites of RH remain to be identified (see Figure 2).

HL and metyrapone contain a ketone group next to their aromatic ring structure. Metyrapone is known to be metabolized via a ketone reductase enzyme in the guinea-pig. Based upon the structural similarity between HL and metyrapone, the formation of RH was studied in human and guinea-pig hepatic microsomal preparations /19/.

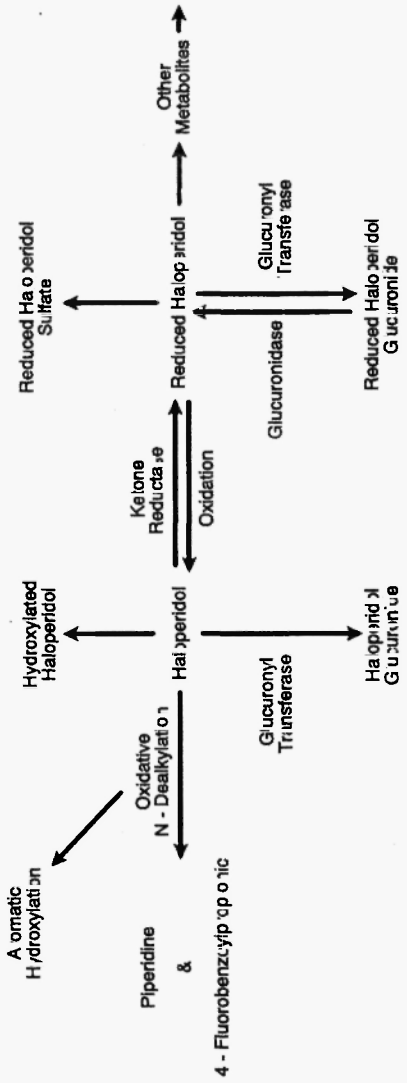


**Fig. 2:** Metabolic profile of haloperidol.

A gas chromatographic assay was developed to measure HL reductase. Incubation conditions either included NADPH (as a cofactor) or did not. The results indicated that the formation of RH requires the ketone reductase enzyme and that NADPH is also needed as a cofactor. Further, known ketone reductase inhibitors, such as menadione, inhibited HL reductase. HL reductase activity was present in guinea-pig cytosol and microsomes while only human hepatic cytosol demonstrated activity.

The oxidation pathway from RH to HL was also examined with human hepatic microsomes /20/. As with the reduction pathway, NADPH was found to be required as a cofactor for oxidation. Quinidine, a specific prototype inhibitor of cytochrome P450 2D6, was added to the microsomal preparations. The oxidation of RH to HL was competitively inhibited by quinidine. Therefore, this indirect method suggests that the reversible metabolic process of RH to HL could be under the influence of the cytochrome P450 2D6 isoenzyme.

Eddington and Young /21/ described high concentrations of RH-glucuronide in the plasma and biliary tract of guinea-pigs. The authors suggest that enterohepatic recycling of RH to RH glucuronide with subsequent release of the RH molecule can also explain the prolonged kinetics of RH. Conjugation by glucuronidation would be under the influence of another set of metabolic enzymes - the UDP glucuronosyl-transferase system /22/. A similar or perhaps identical enzyme system could be involved in the metabolism of HL to HL-glucuronide.

Despite the differences in amount of RH glucuronide formed, the guinea-pig is probably the most appropriate model that can be used when investigating reversible metabolism of HL and RH.

## PHARMACOLOGIC PROPERTIES OF RH

Earlier studies measuring HL plasma concentrations have noted equal or higher concentrations of RH in HL-treated psychiatric patients /23/. In post-mortem brain tissue of nine schizophrenics treated with HL, all patients had equal or greater concentrations of RH compared to HL /24/. In non-specific dopamine receptor binding affinity studies in rat striatal tissue, RH was reported to be 1/400 less potent than HL /25/. However, RH was noted to have a 1/85 lower binding affinity for dopamine $D_2$-receptors compared to HL but had an equal binding affinity for sigma opiate receptors (RH 5.1 nM vs

HL 2.7 nM) /26/. In electrophysiological studies, RH was shown to be an inactive neuroleptic as HL antagonized dopaminergic inhibition of caudate neurons and cerebellar Purkinje neurons induced by noradrenaline while RH was ineffective /27/.

RH was reported to be about 25% as active as HL in apomorphine induced stereotypy despite equal concentrations of the two agents (24 ng/ml vs 25 ng/ml) 1 hour post drug administration /28/. In suppressing amphetamine-induced locomotor activity, RH 0.1 mg/kg was also approximately 25% less effective than HL 0.1 mg/kg (Jann MW, unpublished data).

The biochemical profile of RH is intriguing. RH (0.68 μmol/kg) was reported to be one quarter as potent as HL (0.18 μmol/kg) in producing prolactin stimulation to 100 ng/ml /29/. However, at doses of RH equal to or greater than 1.0 μmol/kg, RH was equivalent to HL in stimulating prolactin release. It is well known that acute administration of neuroleptics results in an increase in the dopamine metabolite homovanillic acid (HVA) concentration in the brain /30/. RH 1.0 mg/kg was shown to be equivalent to HL 0.2 mg/kg in elevating HVA concentrations in the rat prefrontal cortex and caudate /31/. The increased levels in the HVA concentration profile over the following 6 hours were similar for both compounds. These effects were also shown to be possibly dose-dependent, as increasing RH doses from 0.1 mg/kg to 5 mg/kg produced consistent elevations in HVA prefrontal and caudate levels /32/. At higher doses of 10 mg/kg RH resulted in a dramatic decrease in HVA levels in the prefrontal cortex. This pattern was observed with HL, but only with lower doses (5 mg/kg). These partial effects of RH on behavioral paradigms and its biochemical effects could be related to its back conversion to HL.

In animal toxicity studies, HL 10 mg/kg and 50 mg/kg produced moderate and severe sedation, respectively. However, RH at the same doses resulted in moderate sedation and 40% fatality, respectively. When different amounts (3.7, 9.3 and 18.6 nmol) of RH were administered directly into the left red nucleus of the rat brain, all three doses resulted in a marked deviation in the head angle /26/. This model was suggested to closely resemble dystonic reactions in humans. A higher incidence of extrapyramidal side effects was observed in haloperidol-treated psychiatric patients with elevated RH plasma concentrations and RH/HL ratios /33,34/.

## PHARMACOKINETICS AND PHARMACODYNAMICS OF HL AND RH

### Guinea-pig studies

HL and RH 0.5 mg/kg were administered intraperitoneally to guinea-pigs (N=5-6 per group) with HL and RH plasma concentrations obtained at baseline, 10, 30, 60, 120, 180 and 240 minutes post-injection /35/. Maximal RH concentrations ($C_{max}$) were observed 60 minutes post HL administration. Interestingly, HL $C_{max}$ after RH administration occurred later, at 120 minutes. When blood samples were obtained during a 48 hour time period, the mean residence times (MRT) for single doses of 1 mg/kg of HL and 1 mg/kg of RH were 74 minutes and 398 minutes, respectively /36,37/. In another study, HL and RH plasma concentrations were obtained daily for 3 days in guinea-pigs (N=5) receiving intraperitoneal HL and RH. The dosages used for HL and RH were 0.1 mg/kg and 1.0 mg/kg respectively /38/. RH/HL ratios were shown to be dose and time-dependent. The 1.0 mg/kg dose resulted in greater RH/HL ratios after HL administration after repeated injections. However, diminished RH/HL ratios were observed after RH administration with the higher doses. The conversion from HL to RH is suggested to be greater than its back conversion.

### Human studies

Reversible metabolic studies of haloperidol and reduced haloperidol have been conducted in normal healthy volunteers and psychiatric patients. As previously mentioned, in order to examine reversible metabolism, it is necessary to administer both the parent compound and its metabolite. The oxidation of RH to HL has only been investigated in human studies with oral administration of RH. RH has not been administered intravenously or intramuscularly to humans due to formulation issues and for ethical reasons.

The formation of RH from single dose intravenous and oral administration of HL was investigated in six psychiatric patients /39/. The dosages used for intravenous and oral administration were 0.125 mg/kg and 0.5 mg/kg, respectively. Blood samples (N=17) were obtained up to 72 hours post-drug administration. RH plasma concentrations were detected in only one patient and concentrations were not measurable until 30 minutes post intravenous administration. From the oral route, RH plasma concentrations were detected within

15 minutes in all six patients. In the one patient with RH levels measured in both oral and intravenous administration, the elimination half-life of RH was longer with the intravenous route than for the oral route (95.4 hours versus 52.6 hours). This difference could be explained by the rapid metabolism of haloperidol to other inactive metabolites or perhaps by a lack of reductase enzyme in the periphery. Intravenous HL pharmacokinetic parameters, shown in Table 1, resemble those found in previous investigations /39-43/.

In normal healthy volunteers (N=28) administered a single oral 5 mg dose of haloperidol, only 6 subjects had detectable RH plasma concentrations /44/. Maximal RH concentrations ($C_{max}$) were less than 0.5 ng/ml and the time to $C_{max}$ ranged from 8 to 28 hours. The authors noted the wide intersubject variation between HL and RH plasma concentrations.

The reversible metabolic process was first characterized in schizophrenic patients administered a single 10 mg dose of HL and RL /6/. The low clearance parameters for the interconversion are shown in Table 2. The total CL for HL ($CL_{1,0}$ + $CL_{1,2}$) of 1.5 ± 0.32 l/kg closely resembles CL parameters observed by other investigators /15/. The total CL of RH was lower than that of HL, which indicates a longer elimination half-life. The calculated elimination half-life for RH of 71.8 ± 61.2 hours /6/ was also similar to previous investigations, which noted 73.2 ± 29.4 hours /45/. The reduction pathway accounted for approximately 23% of HL biotransformation to RH with a smaller amount being oxidized back to HL. This portion of the HL/RH reduction/oxidation cycle suggests a close parallel between the guinea-pig model and its metabolism in man /35,38/.

When a higher dosage, 0.5 mg/kg (25-36 mg), of HL and RH was given in another seven schizophrenic patients, the CL parameters shifted without a significant change in total CL, as shown in Table 2 /46/. The CLs for reduction and oxidation were higher; approximately 31% of HL was converted to RH but the back conversion increased to about 42% of the total metabolism of RH. Interestingly, the back conversion of RH ($CL_{2,1}$) was almost equivalent to its elimination from the central compartment. These results suggest that the reversible metabolic processes for HL and RH could be dose-dependent.

Ten mg daily of HL and RH were administered to eight schizophrenic patients for 10 days with a two-week washout period

TABLE 1

Summary of the pharmacokinetic parameters of a single dose of haloperidol administered intravenously (results are presented as means ± SD)

| Dose (mg/kg) | T1/2a (hrs) | T1/2 (hrs) | Vd (L/kg) | CL (L/hr) | Reference |
|---|---|---|---|---|---|
| 0.125 mg/kg | 0.14±0.09 | 54.8±21.8 | 21.1±5.4 | 23.4±5.0 | 39 |
| 1.5-5.0 mg | 0.23±0.17 | 18.8±4.7 | 9.5±1.9 | 33±7.8 | 40 |
| 10 mg | 0.19±0.10 | 14.1±3.2 | 1260* | N.R. | 41 |
| 0.125 mg/kg | 0.19±0.07 | 26.2±8.0 | 21.7±6.9 | 49.2±12.0 | 42 |

**TABLE 2**

Summary of reversible metabolic clearance (l/kg) for haloperidol (HL) and reduced haloperidol (RH) (means ± S.D.)

| Dose | $CL_{1,0}$ | $CL_{2,0}$ | $CL_{1,2}$ | $CL_{2,1}$ | Total HL $CL(1,0+1,2)$ | Total RH $CL(2,0+2,1)$ |
|---|---|---|---|---|---|---|
| 10mg[1] | 0.94 ±0.50 | 0.59 ±0.50 | 0.21 ±0.07 | 0.17 ±0.17 | 1.15 ±0.32 | 0.76 ±0.54 |
| 0.5mg/kg[2] (25-36mg) | 0.74 ±0.36 | 0.37 ±0.20 | 0.35 ±0.19 | 0.32 ±0.18 | 1.04 ±0.42 | 0.67 ±0.29 |

[1]Adapted from /6/.
[2]Adapted from /46/.

between the two compounds /38/. Patients had not received antipsychotic medications for at least four weeks prior to HL or RH administration. Plasma RH/HL ratios after HL treatment were significantly higher (0.51 ± 0.12) than HL/RH ratios post RH administration (0.16 ± 0.04; $p<0.005$).

Previous investigations measuring plasma HL concentrations noted a wide interpatient variation between dose and plasma HL levels /15/. The reversible metabolic process could assist in explaining the large interpatient variability. In another study with seven schizophrenics, each patient was given a single dose of 0.5 mg/kg HL and RH and the CL parameters were determined /47/. Four weeks after the single dose phase, 10 mg HL twice a day was given for four weeks. Blood samples were obtained on days 7, 14, 21 and 28. The data combining the single dose CLs and steady-state HL and RH plasma concentrations are shown in Table 3. At steady-state HL Cp noted at day 28, patients 6 and 7 had lower HL Cp than the remaining patients. However, RH Cp also varied between patients. When combining the HL and RH Cp and the CL parameters obtained from the reversible metabolic model, an explanation for these variations can be proposed. For example, in patient #1, the $CL_{10}$ for HL appears to be the main route of metabolism with very little RH formed and oxidized back to HL. On the other hand, very little HL is metabolized via $CL_{10}$ in patient #3. A large RH formation via $CL_{12}$ is observed with a very low back conversion to HL. This would account for the high HL and RH plasma concentrations. Finally, in patient #6, with the lowest HL Cp, the total CL ($CL_{1.0} + CL_{1,2}$) is the highest in this patient group. The total CL parameters for RH are similar to the other patients (except #1) which accounts for the moderate RH Cp measured.

As previously mentioned, a non-linear relationship between HL and RH Cp was noted in over 100 schizophrenic patients /13/. When given a single dose of HL and RH, the RH/HL ratio at the maximum plasma concentration ($T_{max}$, 1-2 hours) was lower than the steady-state RH/HL ratio obtained at the trough time ($C_{min}$) at 12 hours post-dose administration: 0.29 ± 0.29 vs 0.48 ± 0.32, $p<0.005$ /58/. With steady-state data, as the HL dosages increased, RH/HL ratios increased with ratios greater than 1 occurring with HL ≥ 50 mg/day /13/. This single dose study suggests a saturable metabolic process between RH and HL.

**TABLE 3**

Summary of haloperidol and reduced haloperidol plasma concentrations obtained on day 28 and CL (l/kg) parameters from single dose administration

| Subject | HL Cp (ng/ml) | RH Cp (ng/ml) | RH/HL ratio | CL 1,0 | CL 1,2 | CL 2,0 | CL 2,1 |
|---|---|---|---|---|---|---|---|
| 1 | 19.5 | 4.4 | 0.23 | 0.82 | 0.06 | 0.19 | 0.06 |
| 2 | 18.7 | 4.6 | 0.25 | 1.17 | 0.32 | 0.16 | 0.44 |
| 3 | 20.0 | 12.9 | 0.65 | 0.05 | 0.34 | 0.48 | 0.11 |
| 4 | 18.0 | 6.0 | 0.33 | 0.69 | 0.41 | 0.70 | 0.52 |
| 5 | 18.4 | 5.7 | 0.31 | 0.71 | 0.16 | 0.24 | 0.32 |
| 6 | 11.3 | 6.3 | 0.56 | 1.05 | 0.62 | 0.47 | 0.32 |
| 7 | 15.3 | 7.2 | 0.47 | 0.70 | 0.53 | 0.32 | 0.46 |

*Adapted from /46/.

## CLINICAL IMPLICATIONS

Numerous investigations have compared clinical response and haloperidol plasma concentrations. Most investigators have reported a therapeutic "window" between 4-26 ng/ml /59/. Only a small number of clinical investigations examined the relationship between RH and HL plasma concentrations and patient response. These are shown in Table 4. In a preliminary observation with five patients, one patient appeared to show improvement with HL treatment when the RH/HL ratio was less than 1.0 /50/. However, HL dosages were higher than 0.51 mg/kg/day and most patients were above the suggested therapeutic range. In a retrospective study with schizophrenic patients, patients were divided into two groups based upon RH/HL ratio of either <1.0 or >1.0 /51/. In both groups, HL Cp did not differ, but the RH Cp was significantly lower in the <1.0 group ( 2.75, $p<0.01$). Patients were evaluated by the Clinical Global Impression Scale (1 improved, 5 worse). An improved therapeutic effect was observed with the RH/HL <1.0 group vs >1.0 group ($2.81 \pm 1.08$ vs $3.36 \pm 0.95$; $t=2.00$; $p<0.05$).

Eighteen schizophrenics were treated with HL (6-21 mg/day or 0.2 mg/kg/day) for 4 weeks /52/. At the end of the four-week period, HL and RH Cp were determined. Patients were evaluated by the Brief Psychiatric Rating Scale (BPRS) in which response was defined as a greater than 20% improvement in BPRS scores. It was noted that patients rated as improved had RH/HL ratios of 0.94 versus non-responding patients with a ratio of 2.87. Conley *et al.* reported similar results with patients and also noted that RH Cp was associated with increased extrapyramdial side effects /53/.

In a fixed dose trial for 28 days, HL and RH Cp were compared with clinical response in thirteen schizophrenics /54/. Despite the low 10 mg HL dose, moderate HL and RH Cp were detected and RH/HL ratios ranged between 0.77 and 7.55. No correlation between HL Cp or total HL + RH Cp and response were determined; however, RH Cp appeared to correlate with improvement ($r=0.582$, $p=0.040$). The results should be interpreted with caution as this study had a very small sample size.

RH/HL ratios alone may not fully explain a patient's therapeutic response to HL therapy. Schizophrenics were treated with conventional HL doses for 4-6 weeks and evaluated with the BPRS scale /55/. Stepwise multiple regression analysis showed that the

TABLE 4

Summary of clinical studies comparing haloperidol and reduced haloperidol and clinical response (means ± S.D.)

| N | HL Dose | HL Cp(ng/ml) | RH Cp(ng/ml) | RH/HL ratio | Comments | Reference |
|---|---|---|---|---|---|---|
| 5 | 0.51-1.51 mg/kg/day | 13.7-98.3 | 10.2-221.7 | 0.19-4.68 | 1 patient with RH/HL <1.0 appeared to respond. | 49 |
| 41 | 44.5±22.9<br>35.4±17.6 mg/day | 24.4±13.3<br>18.2±14.3 | 40.3±24.9<br>10.6±14.3 | >1.0(N=17)<br><1.0(N=24) | Patients were split into 2 groups; RH/HL <1.0 had greater improvement | 50 |
| 18 | 0.2 mg/kg/day | N/A | N/A | 2.87±2.40<br>0.94±0.35 | Patients with high ratios had <20% response in BPRS scores. | 51 |
| 24 | 10,20 or 30 mg/day | N/A | N/A | N/A | RH Cp reported to decrease response. | 52 |
| 13 | 10mg/day | 6.8±4.8 | 13.0±1.8 | 2.7±2.0 | Correlation with RH Cp reported with response. | 53 |
| 15 | 0.4 mg/kg/day | 7.2-39.4 | 2.2-52.9 | Reported as HL/RH | Positive correlation between HL/RH red blood cells levels and response. | 54 |
| 30 | 0.4 mg/kg/day | N/A | N/A | N/A | No correlation with ratios and response. | 55 |
| 12 | 20 mg/day | 14.6±4.4<br>17.5±8.9 | 5.3±3.4<br>3.2±2.7 | 0.38±0.26<br>0.17±0.09 | Patients with higher ratios had greater response. | 56 |
| 29 | 0.51±0.2 mg/kg/day | 24.2±14.5 | 19.2±18.8 | N/A | No correlation with RH/HL ratios and response. | 57 |

N/A = not reported
Cp = Plasma level
HL = Haloperidol
RH = Reduced Haloperidol

duration of illness and RH/HL ratios could account for 82% of the variation in response. Patients who had no improvement had a longer duration of illness (10.4 ± 8.2 years) and a higher RH/HL ratio (1.9 ± 1.7) compared to patients who showed improvement (6.4 ± 5.2 years and 0.9 ± 1.1). In a double-blind placebo controlled study, 0.4 mg/kg/day HL was given to patients for six weeks. RH and HL Cp and concentration in red blood cells (RBC) were obtained and patients were evaluated by the BPRS in the 6th week. No correlations were found between clinical response and the following: HL Cp; RH Cp; HL + RH Cps; HL + RH RBC concentrations, and HL/RH Cp ratios. The investigators reported a significant correlation between negative symptoms and HL/RH RBC concentrations ($r=0.63$, $p=0.011$).

Instead of grouping patients according to the RH/HL ratios, Kirch *et al.* divided subjects into two groups: by HL Cp of either 5-15 ng/ml or >15 ng/ml /56/. The study duration was six weeks with total HL dose ranging between 18-38 mg/day. No correlation was found between BPRS scores and RH/HL ratios ($r=0.15$) in either group. In Chinese schizophrenics, patients with HL response had slightly higher RH/HL ratios compared to non-responding patients /57/. Kelly *et al.* /58/ divided HL treated patients into two groups based upon HL Cp: 8-18 ng/ml and >25 ng/ml. The patients were part of a larger study and were treated for a two-week period. The patients could be classified as extremely ill as the minimum BPRS score was 62 and the maximum 101. No correlations were found between RH/HL ratios and clinical response.

In these previous studies /56-58/, it is not surprising that a lack of correlation was found between RH/HL ratios, RH Cp and clinical response. When a suggested therapeutic range of 5-15 ng/ml and >15 ng/ml or 8-18 ng/ml and >25 ng/ml are used for HL Cp, this does not account for the wide interpatient variability observed with HL and RH metabolism. RH Cp could be elevated in all HL Cp groups. Most studies agree that a minimum of four weeks is required to achieve the full benefit of antipsychotic therapy and two weeks is too short a period. Finally, the elevated BPRS scores could indicate a subgroup of schizophrenic patients refractory to typical antipsychotics including HL, so that RH/HL ratios, HL Cp and RH Cp measurements may be meaningless. As noted in previous sections, Chinese patients appear not to produce RH as do other ethnic groups and the HL dose was below 40-50 mg/day. Therefore, a comparison between responders and non-responders in Chinese patients is difficult.

## CONCLUSIONS

Numerous compounds undergo a reversible metabolic process. The possible clinical effects of reversible metabolism are under-appreciated due to the complexity of administering the metabolite and the parent drug in the proper animal model or in humans. Mathematical models have been devised to calculate linear versus non-linear disposition. However, other factors complicating the reversible process include the partial or full pharmacologic activity of the metabolite(s). Mathematical modelling of reversible metabolism was delineated by the prednisone-prednisolone studies. HL and its reduced metabolite have recently been demonstrated to undergo a reversible process. The clinical implications of HL and RH interconversion have been examined in schizophrenics; however, its clinical application requires further evaluation.

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