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REVIEW

A review of the pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers

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Amisulpride binds selectively to dopamine D_2 and D_3 receptors in the limbic system. Low doses of amisulpride preferentially block presynaptic D_2/D_3-dopamine autoreceptors, thereby enhancing dopaminergic transmission, whereas higher doses block postsynaptic receptors, thus inhibiting dopaminergic hyperactivity. Amisulpride is clinically effective on the negative symptoms of acute schizophrenia exacerbations at low dosages (50–300 mg/day), and also on the positive symptoms of the disease at high dosages (400–800 mg/day). Nineteen clinical studies involving 358 volunteers have investigated the pharmacokinetics, pharmacodynamics and tolerability of amisulpride. Amisulpride shows linear pharmacokinetics, a bioavailability of 48%, low protein binding (17%) and an elimination half-life of $\sim$12 h. It is predominantly eliminated in the urine as the parent compound. It exhibits no significant detrimental effects in psychometric or memory tests up to the dose of 400 mg/day, inducing only mild impairment at high doses, whereas EEG data suggest an alertness-enhancing effect at low doses ($\leq$50 mg). Moreover, amisulpride does not potentiate the depressant effects on the central nervous system of alcohol and lorazepam. This tolerability profile is clearly better than that of haloperidol 4 mg/day and is consistent with a weak blocking effect on striatal D_2 receptors. In summary, studies in humans have shown that amisulpride is free of behavioural toxicity at doses exerting clear antipsychotic efficacy and confirm that its CNS effects may vary with the dose administered.

KEY WORDS — amisulpride; healthy volunteers; pharmacokinetics; pharmacodynamics; tolerability

INTRODUCTION

Amisulpride, a substituted benzamide, selectively blocks cerebral dopamine D_2 and D_3 receptors (Sokoloff *et al.*, 1992; Schoemaker *et al.*, 1997). In vivo it shows a higher affinity for limbic than striatal dopamine receptors, which points to a favourable neurological safety profile in humans (Schoemaker *et al.*, 1997). In addition, low doses of amisulpride preferentially block presynaptic D_2/D_3-dopamine autoreceptors, thereby facilitating dopamine transmission, whereas higher doses block postsynaptic D_2/D_3-dopamine receptors, thus inhibiting dopaminergic hyperactivity (Perrault *et al.*, 1997). This novel dual dopamine receptor-blocking effect is consistent with the improvement of the negative symptoms of schizophrenia at low dosages (50–300 mg/day) of amisulpride and of the positive symptoms at higher dosages (400–800 mg/day).

Our objective was to review non-therapeutic trials of amisulpride in order to investigate its pharmacokinetics, pharmacodynamics and tolerability, both in healthy volunteers and in certain categories of non-psychotic at-risk patients.

The significance and safety of pharmacological studies on antipsychotics carried out in volunteers have been questioned in recent years. However, interest in such studies returned with the recent availability of new antipsychotics, including amisulpride, and of new investigative techniques, such as positron emission tomography (PET). Moreover, a consensus conference convened by the British

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Association of Psychopharmacology (BAP) recently issued a set of guidelines regarding studies of antipsychotics in healthy volunteers, stating that such studies may be useful for the following three main reasons: (1) studies in healthy humans bridge the gap between animal laboratory experiments and clinical trials in patients, allowing the investigation of drug actions in human beings without the confounding effects of illness-related factors; (2) although it is a widespread belief that volunteers are more sensitive than patients to antipsychotics, this has not been definitely established, and the differences that have been reported may well be the consequence of methodological variations, including acute or chronic dosing conditions; (3) useful pharmacodynamic information can be derived from EEG recordings, cognitive testing and PET studies in healthy volunteers (King and the BAP Consensus Group, 1997).

The pharmacological studies of amisulpride in humans aimed to investigate: (1) its pharmacokinetic characteristics (absorption, distribution, metabolism and excretion) in healthy young volunteers and in at-risk groups of subjects (aged subjects, renally impaired patients); (2) its pharmacodynamic profile, including its effects on psychomotor and memory performances, body sway and pharmaco-EEG; and (3) its clinical tolerability.

METHODS

Nineteen clinical studies of the pharmacology of amisulpride (13 on pharmacokinetics and metabolism, six on pharmacodynamics) have been performed on a total of 358 subjects. Of these subjects, 288 were aged between 18 and 40 (mean age $\pm$ SD $= 25 \pm 4$ years; mean weight $\pm$ SD $= 71 \pm 9$ kg), 37 were aged more than 65 years (69 ± 4 years; 68 ± 9 kg) and 33 were renally impaired patients (52 ± 15 years; 67 ± 14 kg; creatinine clearance 80–50 mL/min: 6 patients, 50–20 mL/min: 11 patients, 20–10 mL: 10 patients, < 10 mL/min: 6 patients).

All the studies assessing the pharmacodynamic characteristics of amisulpride were double-blind, crossover, placebo-controlled studies involving single or multiple daily oral administrations at doses ranging from 50 mg to 400 mg. The studies used a comprehensive battery of validated objective and subjective tests that are commonly used in psychopharmacological studies and that are capable of detecting minor changes in vigilance and memory performance. The battery comprised tests exploring psychomotor performance and attention (critical flicker fusion threshold [CFFT], choice reaction time [CRT], critical tracking task [CTT], divided attention task [DAT], continuous performance task [VIG], tapping, body sway), information processing (arithmetic calculation, digit symbol substitution test [DSST], syntactic reasoning, Stroop test), memory (working memory, word or picture list for declarative memory, word item completion for implicit memory, tower of Toronto for procedural memory), EEG recordings, and subjective evaluations (Stanford Sleepiness Scale, Bond and Lader visual analog scales [VAS] for alertness, Addiction Research Center Inventory [ARCI] for drug-related feelings (Haertzen, 1966), 'subjective well-being under neuroleptics' scale [SWN] (Naber *et al.*, 1994), and schizophrenia positive and negative symptoms scale [PANSS] (Kay, 1991).

All studies were approved by an independent ethics committee, and all participants gave their informed written consent prior to study entry.

RESULTS

Pharmacokinetics

The main pharmacokinetic characteristics of amisulpride, as previously reported by Coukell *et al.* (1996), are summarised in Table 1.

The profile established by pooling all data from pharmacokinetic studies reveals no dose dependency of amisulpride:

- half-life, renal clearance and amount excreted in urine as unchanged amisulpride are the same regardless of the dose administered;
- $AUC_{(0-\infty)}$ increases as a function of the dose;
- C_{max} is the parameter of greatest variability, possibly because of the complex absorption pattern;
- in patients receiving up to 1200 mg/day, trough plasma levels are proportional to the dose.

Absorption. The absolute bioavailability of the 50 mg tablet is $\sim$50% (range 48–51%). Absorption is rapid. Two plasma concentration peaks are generally observed, the first peak occurring approximately 1 h after oral administration.

Distribution. Distribution volume of amisulpride is 5.8 L/kg (SD 0.4 L). Amisulpride shows a weak affinity for plasma proteins (17%), suggesting a low risk of interaction with coadministered drugs.

Excretion and metabolism. Amisulpride is primarily excreted in urine: at doses of 50–200 mg, almost 50% of an intravenous dose and 22–25% of an oral

Table 1. Summary of the pharmacokinetics of amisulpride in young healthy volunteers after oral administration of a 50 mg dose (N = sample size)

Absorption ($N=61$)	T_{max} 1 (h) median value	1.0
	C_{max} 1 (ng/mL)	42.3 ± 3.3
	T_{max} 2 (h) median value	4.0
	C_{max} 2 (ng/mL)	55.7 ± 3.7
	F (%)	48–51
Distribution ($N=18$)	Vdb (L/kg)	5.8 ± 0.4
	Free fraction (%)	84
Excretion ($N=4$)	Total radioactivity excreted in urine (i.v. route) (%)	75.4 ± 2.9
	Total radioactivity excreted in faeces (%)	20.0 ± 2.1
	Amount excreted unchanged (i.v. route) (%)	49.2–55.1
Metabolism	Low metabolism: oxidation of the pyrolidine rings, N-deethylation and hydroxylation	
Elimination ($N=78$)	Open two-compartment model	
	$T_{1/2\alpha}$ (h)	1.3 ± 0.1
	Apparent $T_{1/2\beta}$ (h)	7.0–7.9 (i.v. route) 11.7 ± 0.5 (oral route)
	Plasma systemic clearance (L/h)	31.2–41.6
	Plasma renal clearance (L/h)	17.7 ± 4.5
	No modification of PK profile following repeated once-daily administration	
Influence of pathophysiological conditions	Variable effect of food (maximum decrease: 40%) Clearance reduction by age Clearance reduction by renal impairment	
Interactions	No reciprocal interaction with lorazepam Alcohol increases AUC of amisulpride by 10–20%	

dose are recovered in urine as the unchanged compound. Renal clearance, which ranges from 17 to 20 L/h (330 mL/min), exhibits very little variation with the dose administered but does correlate with creatinine clearance. Drug clearance is reduced in renally impaired patients, and also in elderly subjects, probably owing to age-related reduction in renal function. Amisulpride undergoes only minimal metabolic transformation. After oral administration of radiolabelled amisulpride, all the radioactivity found in plasma is attributable to unchanged amisulpride. Similarly, the radioactivity excreted in urine and faeces relates almost solely to the unchanged compound. The pharmacokinetic profile of amisulpride remains unchanged after repeated daily administrations of a 200 mg dose for 7 days. Antipyrine half-life is not altered after repeated administration, which suggests the absence of inducing or inhibiting effects on hepatic microsomal enzyme activity. Only a small amount of amisulpride is removed from the circulation after a 3 h haemodialysis session.

Elimination. The value of $T_{1/2\alpha}$ reported in Table 1 was determined after intravenous administration, using a two compartment model. As previously reported (Coukell *et al.*, 1996), elimination is also biphasic after oral administration and can be described by an open two compartment model. However, because of the difficulty in modelling the absorption phase (due to the two plasma concentration peaks), determination of the initial elimination phase is not always correct. Hence, only the terminal elimination phase can be calculated accurately.

Pharmacokinetics of amisulpride enantiomers. After administration of amisulpride, which is a racemate, either by the oral or the intravenous route, plasma concentration profiles of (S)- and (R)-enantiomers are parallel, with constantly higher concentrations of the (S)-enantiomer (Figure 1). The (S)- and (R)-enantiomers are in the ratio of ~ 1.3 for C_{max} and AUC, whatever the administration route. Enantiomer pharmacokinetics are not altered after repeated oral administrations in healthy volunteers (Le Bricon *et al.*, 1996) or in aged subjects.

Interactions. The risk of drug-drug interactions is limited, owing to the low levels of plasma protein binding and metabolism. Furthermore, amisulpride was not shown to affect the activity of the main

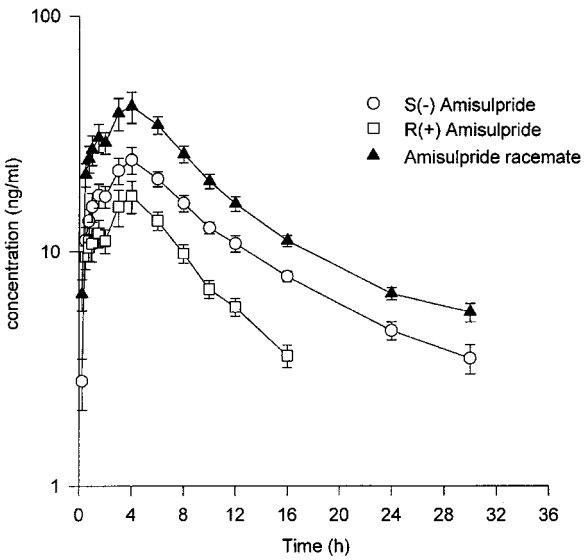

Figure 1. Mean plasma concentration profiles of amisulpride racemate amisulpride and the (S)- and (R)-enantiomers after a single oral administration of 50 mg amisulpride to 18 healthy young volunteers. Reproduced with permission from Le Bricon *et al.*, 1996. Pharmacokinetics of amisulpride and its enantiomers after single and repeated doses in healthy volunteers. *Eur J Drug Metab Pharmacokinet* (Special issue): 135–136. Copyright © European Journal of Drug Metabolism and Pharmacokinetics

human CYP 450 enzymes. Potential interactions with alcohol have been studied during the course of the pharmacodynamic studies. Results suggest a moderate increase in amisulpride absorption (10–20% increase in plasma concentration) by the concomitant ingestion of alcohol. No interaction with lorazepam was observed.

Psychomotor performance and attention

Single administrations of a low dose of amisulpride (50 mg) have been shown to be without clinically significant detrimental effects in a wide range of psychometric tests intended to explore attention, vigilance, sensory-motor coordination and information processing (Table 2), as well as body sway. Furthermore, a 4 day treatment with repeated daily doses of 50 mg amisulpride showed no detrimental effects, compared with placebo, in several tests (including a tracking task) administered to subjects in a sleep-deprivation state, a condition known to potentiate the sedative effects of drugs acting on the central nervous system (CNS) (Patat *et al.*, 1999). A significant improvement in hand steadiness was also observed after five daily doses of 50 mg amisulpride (Ramaekers *et al.*, 1999).

Table 2. Central effects of a single oral dose of amisulpride or haloperidol as assessed in various psychomotor and performance tests in young volunteers (Ramaekers *et al.*, 1999; Peretti *et al.*, 1997) and in elderly volunteers (Legangneux *et al.*, 2000)

	Amisulpride				Haloperidol			
Test	50 mg	100 mg	200 mg	400 mg	1 mg	2 mg	4 mg	Reference
Choice reaction time (CRT)	0		0			0		Legangneux *et al.*, 2000
	0	0			0	0		Peretti *et al.*, 1997
	0			0			↓	Ramaekers *et al.*, 1999
Critical tracking task (CTT)	0		0			0		Legangneux *et al.*, 2000
	0			0			↓	Ramaekers *et al.*, 1999
Divided attention task (DAT)	0			0			↓	Ramaekers *et al.*, 1999
Continuous performance task (VIG)	0		0			(↓)	↓	Ramaekers *et al.*, 1999
Tapping	0	0			0	0		Peretti *et al.*, 1997
Digit symbol substitution test (DSST)	0	0			0	0		Peretti *et al.*, 1997
	0			0			↓	Ramaekers *et al.*, 1999

↓, significant impairment vs placebo; 0, no significant change vs placebo; (↓), variation approaching statistical significance.

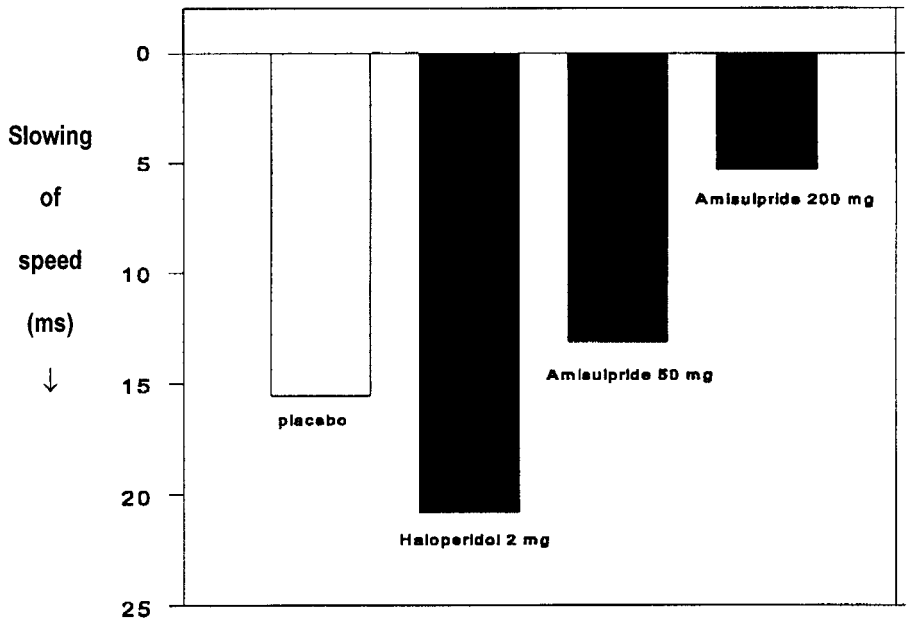

Figure 2. Speed of detection in a digit vigilance task in elderly subjects after single oral doses of placebo, haloperidol 2 mg, amisulpride 50 mg or amisulpride 200 mg (means of post-dosing measurements). Reproduced with permission from Legangneux *et al.*, 2000. The acute effects of amisulpride (50 mg and 200 mg) and haloperidol (2 mg) on cognitive function in healthy elderly volunteers. *J Psychopharmacol* **14**: 164–171. Copyright © Sage Publications Ltd

Single doses of 100 mg and 200 mg amisulpride were also free of deleterious effects on psychomotor performance and body sway (Mattila *et al.*, 1996; Peretti *et al.*, 1997; Perault *et al.*, 1998). In another study (Legangneux *et al.*, 2000), elderly subjects showed a significant ($p < 0.05$) improvement in reaction time in a VIG test (digit vigilance task) after a 200 mg dose (Figure 2).

A single administration of a high dose (400 mg) of amisulpride did not cause any alterations in selective and divided attention, motor activity, sensory–motor coordination or vigilance in healthy volunteers. However, repeated administrations of amisulpride 400 mg/day for 4 days induced significant impairments in several tests, including CTT, CRT, DAT, DSST and VIG (event detection vigilance task) (Figures 3–5) (Ramaekers *et al.*, 1999). Thus, repeated administrations of high doses of amisulpride may entail some sedative effects in healthy volunteers.

Finally, no pharmacodynamic interactions impacting psychomotor performance were detected after the concurrent administration of 50 mg or 200 mg of amisulpride with 0.8 g/kg of ethanol or 2 mg of lorazepam to young subjects (Mattila *et al.*, 1996; Perault *et al.*, 1998). In contrast, haloperidol induced significant impairments in various tasks after single or repeated administrations either to young subjects (deterioration of performance in CTT, DAT and CRT at 3 h and 6 h, and VIG at 4 h and 7 h, after 4 mg (single dose) or 4 mg/day for five days) (Figures 3–5, Table 2) (Peretti *et al.*, 1997; Ramaekers *et al.*, 1999) or to elderly subjects (increase in detection time in VIG 9 h and 24 h after a single dose of 2 mg) (Figure 2) (Legangneux *et al.*, 2000). These marked deleterious effects are at variance with those observed after 400 mg amisulpride in young volunteers or after 50 mg and 200 mg in elderly subjects (Ramaekers *et al.*, 1999; Legangneux *et al.*, 2000).

Potential alertness-enhancing effects of a low dose of amisulpride (50 mg/day for 4 days) were assessed in healthy young subjects using a sleep deprivation procedure. Sleep deficiency is known to impair flexibility and perseverance, to decrease motivation, to diminish performance in sustained and selective attention tasks, owing to a lowering of the arousal level, and to accelerate performance deterioration over time on a given task. Therefore, sleep deprivation is a recognised model for the investigation of a drug's alertness-enhancing effects. Caffeine was used as a positive control. No detrimental effects of amisulpride 50 mg/day were found in an array of psychomotor performance and cognitive tests

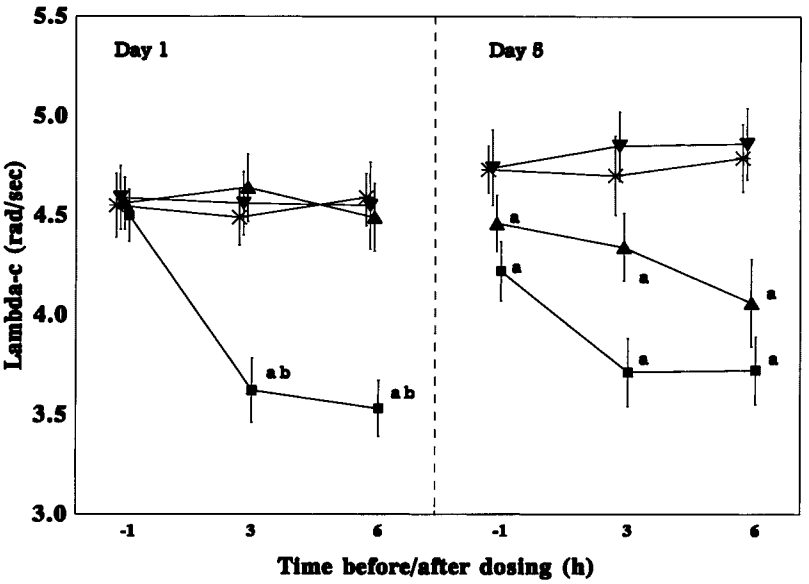

Figure 3. Mean (± SEM) lambda-c (i.e. frequency at which control loss occurs) in the critical tracking task before and after dosing on days 1 and 5 in healthy volunteers. Symbols refer to the following treatments: ×, placebo; ▼, amisulpride 50 mg/day; ▲, amisulpride 400 mg/day; ■, haloperidol 4 mg/day. **a** and **b** denote a significant difference vs placebo and a significant difference between amisulpride and haloperidol, respectively. Reproduced with permission from Ramaekers *et al.*, 1999. Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. *J Clin Psychopharmacol* **19**: 209–221. Copyright © Lippincott Williams & Wilkins

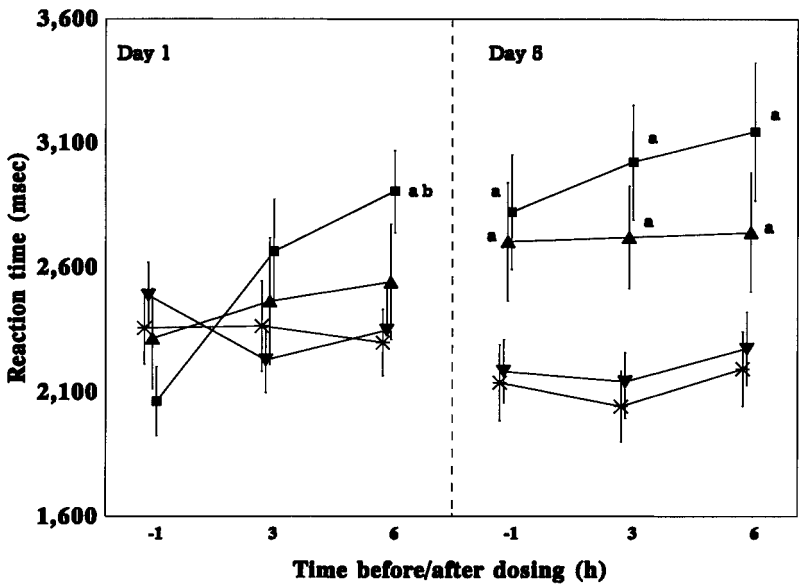

Figure 4. Mean (± SEM) reaction time to peripheral signals in the divided attention task before and after dosing on days 1 and 5 in healthy volunteers (see Figure 3 for description of symbols). Reproduced with permission from Ramaekers *et al.*, 1999. Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with atypical (amisulpride) and a classic (haloperidol) antipsychotic. *J Clin Psychopharmacol* **19**: 209–221. Copyright © Lippincott Williams & Wilkins

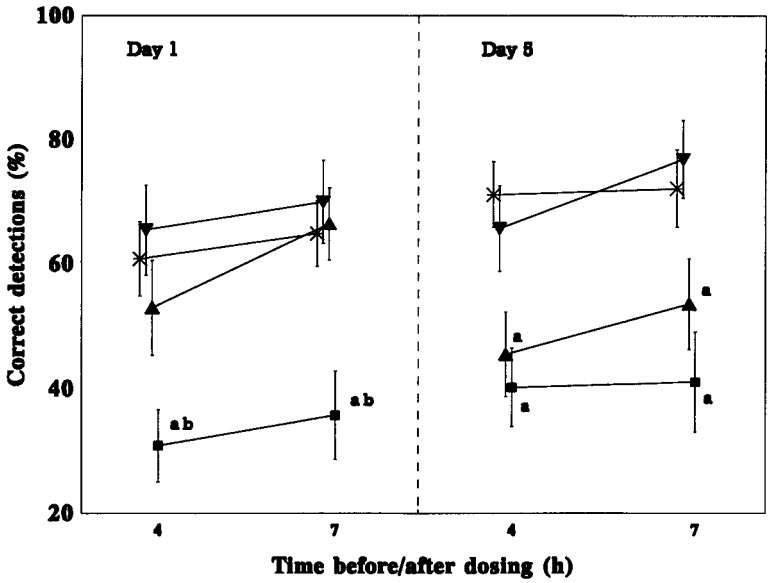

Figure 5. Mean (± SEM) percentage of correct detections in the continuous performance task before and after dosing on days 1 and 5 in healthy volunteers (see Figure 3 for description of symbols). Reproduced with permission from Ramaekers *et al.*, 1999. Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. *J Clin Psychopharmacol* **19**: 209–221. Copyright © Lippincott Williams & Wilkins

carried out in sleep-deprived volunteers. Moreover, subjects' performance after treatment with this low dose of amisulpride was frequently found to be intermediate between those noted after placebo and after caffeine, and the performance improvement intensified at the end of the 4 day treatment period (14 h and 19 h after the last amisulpride dose) (Patat *et al.*, 1999).

Memory

Whichever dose of amisulpride is administered (50, 100, 200, or 400 mg), a single administration is without clinically relevant detrimental effects on working memory (Ramaekers *et al.*, 1999; Legangneux *et al.*, 2000), declarative memory (immediate free recall, delayed free recall, picture or word recognition) (Mattila *et al.*, 1996; Perault *et al.* 1998; Peretti *et al.*, 1997; Legangneux *et al.*, 2000), implicit memory (picture stem completion) (Peretti *et al.*, 1997) and procedural memory (tower of Toronto) (Peretti *et al.*, 1997). However, repeated administrations of amisulpride 400 mg/day to young subjects caused some working memory impairment 3 h and 6 h after dosing, and an increase in reaction time in the syntactic reasoning task, but this effect was notably less than after single or multiple doses of 4 mg of haloperidol (Ramaekers *et al.*, 1999).

No pharmacodynamic interaction impacting memory was noted when amisulpride (50 mg or 200 mg) was administered concurrently with 0.8 g/kg of alcohol or 2 mg of lorazepam (Mattila *et al.*, 1996; Perault *et al.*, 1998).

In contrast, in young subjects, both a single dose and multiple daily doses of haloperidol 4 mg caused significant working memory impairment when compared with placebo and amisulpride 50 mg or 400 mg (Ramaekers *et al.*, 1999). As low a dose as 2 mg of haloperidol may also significantly impair working memory in elderly subjects from 2 h to 12 h after dosing (Legangneux *et al.*, 2000). In addition, 1 mg or 2 mg of haloperidol may induce a significant decrease in procedural memory in young volunteers: while remaining able to acquire a problem-solving routine (despite a mild psychomotor slowing down and some degree of cognitive sluggishness), haloperidol-treated subjects needed significantly more steps than control subjects to achieve the test objective, and some of them routinised a non-optimal solution. Overall, haloperidol-treated subjects are characterised by a low reliability index in solving problems (Peretti *et al.*, 1997).

Electroencephalography

In a double-blind, placebo-controlled trial, Saletu *et al.* (1994) investigated the pharmaco-EEG profile of a single dose of amisulpride (12.5, 25, 50 or 100 mg) in 10 healthy volunteers. EEG analyses revealed only weak and inconsistent effects of amisulpride across the dose range studied. However, some EEG activation, primarily characterised by an increase in fast beta waves, was detected in resting conditions after the administration of 12.5 mg and 25 mg amisulpride. These quantitative EEG changes were less evident after a dose of 50 mg or 100 mg.

In a placebo-controlled study performed in sleep-deprived subjects, EEG recordings obtained in resting conditions were submitted to spectral analysis, in order to assess the potential alertness-enhancing effects of amisulpride (50 mg/day for 4 days) (Patat *et al.*, 1999). Statistically significant ($p \leq 0.05$) increases in total power spectral density, in absolute delta, theta and beta (mainly 12–16 Hz and 30–40 Hz) activities, and in relative beta (30–40 Hz), delta and beta (12–40 Hz) activities over baseline total power, were observed 4 h, 9 h, 14 h and/or 19 h after the last administration of amisulpride, depending on the frequency band and the EEG lead considered (Table 3). There

Table 3. Summary of the statistically significant EEG changes observed in sleep-deprived young volunteers after repeated administrations of amisulpride (50 mg/day for 4 days) or a single dose of slow-release caffeine (600 mg)

Parameter	EEG lead	Amisulpride vs placebo	Caffeine vs placebo
Total power	F4T4, F3T3	↑ (4, 14, 19 h)	0
	T4O2	↑ (19 h)	0
	T3O1	↑ (14, 19 h)	0
	F4T4	↑ (4, 9, 19 h)	↓ (14 h)
Delta absolute power	T4O2	0	0
	T3O1	↑ (9, 19 h)	0
	F3T3	↑ (19 h)	↓ (14 h)
Delta relative power	F4T4, F3T3	0	0
	T4O2, T3O1	0	↓ (14 h)
	F4T4, T4O2	↑ (14, 19 h)	0
Theta absolute power	T3O1	↑ (4, 9, 14, 19 h)	0
	F3T3	↑ (4, 14, 19 h)	0
	F4T4	0	↓ (4 h)
Theta relative power	T4O2, F3T3	0	↓ (9 h)
	T3O1	0	↓ (9, 14 h)
Alpha absolute power	F4T4, T4O2, T3O1	0	0
	F3T3	↑ (4 h)	0
Alpha relative power	F4T4, T4O2, F3T3	0	0
	T3O1	0	↑ (14 h)
Beta (12–16 Hz) absolute power	F4T4	↑ (14 h)	↑ (4, 9 h)
	T4O2	↑ (14 h)	0
	F3T3, T3O1	0	0
Beta (12–16 Hz) relative power	F4T4, T4O2, T3O1, F3T3	0	↑ (4 h)
Beta (16–20 Hz) absolute power	F4T4	0	↑ (4 h)
	T4O2	0	↑ (4 h)
	T3O1	0	0
	F3T3	↑ (19 h)	0
Beta (16–20 Hz) relative power	F4T4, T4O2, F3T3	0	↑ (4 h)
	T3O1	0	↑ (4, 19 h)
Beta (20–30 Hz) absolute power	F4T4, T3O1	0	↑ (4 h)
	T4O2	0	0
	F3T3	↑ (4 h)	↑ (4 h)
Beta (20–30 Hz) relative power	F4T4, F3T3, T3O1	0	↑ (4 h)
	T4O2	0	↑ (4, 19 h)
	F4T4	0	0
Beta (30–40 Hz) absolute power	T4O2	↑ (19 h)	↑ (4, 9 h)
	T3O1	↑ (4, 19 h)	↑ (4, 9 h)
	F3T3	↑ (4, 19 h)	↑ (4 h)
	F4T4	0	↑ (4 h)
Beta (30–40 Hz) relative power	T4O2	0	↑ (4, 9 h)
	T3O1	↑ (4 h)	↑ (4 h)
	F3T3	↑ (4 h)	↑ (4, 19 h)

0, not significant; ↑, significant increase; ↓, significant decrease.

was a trend ($0.05 < p < 0.10$) towards increased spectral activity for all frequency bands and EEG leads at the other time points. Effects on slow delta and theta waves were also observed throughout the study day, with increases of 50–100%, whereas the effects on beta waves predominated at the end of the sleep deprivation period (14–19 h), with increases of about 100% compared with placebo.

Thus, significant improvements or trends toward an improvement in alertness, characterised by increased EEG power in absolute and relative beta waves (12–40 Hz), were observed after administration of amisulpride. Similar changes were also noted after the ingestion of caffeine (two 300 mg slow-release caffeine capsules on the fourth study day), which was used as an active control in the same study. Differences between amisulpride and placebo were mostly apparent at the end of the sleep deprivation period, i.e. 19 h after dosing (Figure 6) (Patat *et al.*, 1999).

Subjective evaluation

Single or multiple doses of amisulpride in the 50–400 mg range do not induce consistent changes in subjective feelings, as assessed by visual analogue scales or by questionnaires (Stanford Sleepiness Scale, ARCI). In most studies, amisulpride did not show any sedative effects at dosages up to 400 mg/day in young subjects or after a single 200 mg dose in elderly subjects (Mattila *et al.*, 1996; Peretti *et al.*, 1997; Perault *et al.*, 1998; Patat *et al.*, 1999; Ramaekers *et al.*, 1999; Legangneux *et al.*, 2000). At dosages up to 400 mg/day, amisulpride did not induce any significant change in the SWN scale score or in the PANSS 'negative symptoms' and 'general psychopathology' subscales scores in healthy volunteers. Of the 13 feelings scored by the psychiatrists, only drowsiness was rated as significantly increased after amisulpride (400 mg/day), compared with placebo (Ramaekers *et al.*, 1999). The lack of consistent sedative effects of amisulpride demonstrated by the subjective assessment confirms the results of the objective tests. It was also observed in sleep-deprived subjects (Patat *et al.*, 1999).

In contrast, single and multiple doses of haloperidol (4 mg/day) or lorazepam (2 mg) used as active controls induced marked and statistically significant sedative effects. These were characterised by an increase in the PCAG (pentobarbitone-chlorproma-

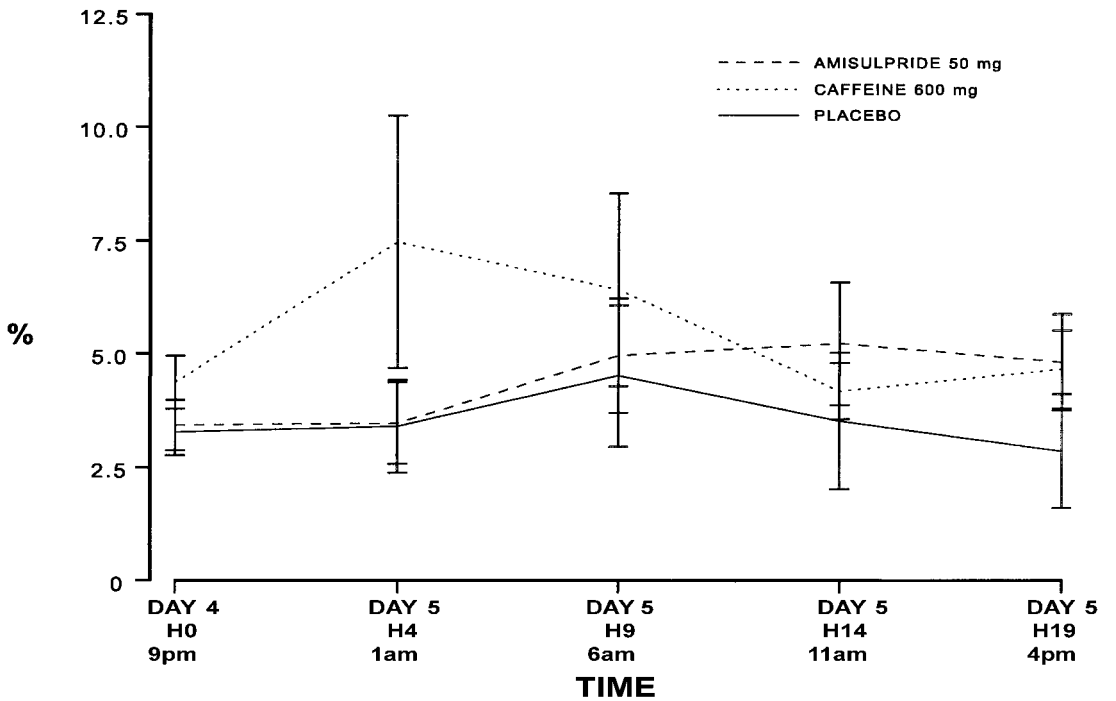

Figure 6. Relative EEG beta (20–30 Hz) activity observed in the T4O2 lead in sleep-deprived young subjects (mean ± SEM). Reproduced with permission from Patat *et al.*, 1999. Effects of 50 mg of amisulpride on EEG, psychomotor and cognitive functions in healthy sleep-deprived subjects. *Fundam Clin Pharmacol* **13**: 582–594. Copyright © Elsevier Science

zine-alcohol group) sedation score and by decreases in the BG (benzedrine group) alertness and AG (amphetamines group) activation/motivation scores of ARCI (from 2 h to 8 h after lorazepam; from 3 h to 6 h after the first administration of haloperidol, and over the whole observation period after five daily doses of haloperidol). Both lorazepam and haloperidol were also associated with significant changes in the MBG (morphine-benzedrine group) euphoria score and in the LSD (lysergic acid diethylamide group) somatic distress (discomfort) score, with similar time courses (Perault *et al.*, 1998; Ramaekers *et al.*, 1999). In addition, in contrast to placebo and amisulpride 50 mg or 400 mg, haloperidol 4 mg/day induced a significant impairment of well-being, which was especially noticeable on the subscale scores of ARCI exploring emotional regulation and mental and physical functioning, as well as on the SWN scale score (Ramaekers *et al.*, 1999). The two PANSS subscales ('negative symptoms' and 'general psychopathology') also revealed significant behavioural impairments with haloperidol, compared with placebo and amisulpride. Finally, based on the psychiatrist's clinical global impression, haloperidol stands out as markedly different from placebo and amisulpride: much more frequent and severe adverse effects occur with haloperidol than with placebo or amisulpride, which may impact the central functions involved in daily activities.

DISCUSSION AND CONCLUSIONS

Pharmacodynamic studies that accurately evaluate a drug's cognitive and psychomotor effects are important in collecting useful information on the safety profile of neuroleptics, i.e. the nature and severity of their adverse effects, the possible relationship between their pharmacodynamic effects and pharmacokinetic parameters, and their mechanisms of action in psychosis. However, studies carried out in schizophrenic patients have failed to demonstrate any consistent effects of typical or atypical neuroleptics on psychomotor and cognitive functions. Obviously, studies in schizophrenic patients are made difficult by a number of confounding factors, including problems in controlling for dosage and duration of treatment, the ethical inadvisability of using an inactive placebo control, the influence of learning and motivation, and factors relating to schizophrenia itself (different clinical subtypes, changes in symptom severity over time, comorbidities, co-medications, etc.) (King, 1990; 1994). Impairments of cognitive function in schizophrenic patients, such as attention and information-processing deficits, intellectual sluggishness and formal thought disorders, complicate the interpretation of drug effects. In addition, the potentiality of neuroleptics themselves to induce negative symptoms remains a matter of controversy.

Conventional antipsychotics exert sedative and anticholinergic side effects and may induce extrapyramidal symptoms (for a review see Heaton and Crowley, 1988). Memory decrements are ascribed to the anticholinergic properties of neuroleptics, and there is some evidence of additional effects on visuomotor integration, attention and global intelligence. One can expect all these effects to impair performance in various psychomotor, cognitive and memory tests. Medalia *et al.* (1988) reported that cognitive functions are differently affected in schizophrenic patients, depending on treatment duration: acute neuroleptic treatment exerts obvious adverse effects on motor and visuomotor skills, whereas longer-term effects include impairments in planning ability and fine motor coordination.

Thus, although the therapeutic efficacy of antipsychotic drugs is well documented, their potential clinical benefits should be weighed against their potential risks. The most common and obvious side effects of standard neuroleptics are extrapyramidal motor control disturbances, i.e. Parkinson-like rigidity, tremor, bradykinesia, akathisia, acute dystonia and tardive dyskinesia. Atypical neuroleptics (e.g. clozapine, risperidone, olanzapine, amisulpride) exhibit no or a much smaller propensity to induce extrapyramidal symptoms than standard neuroleptics. Nevertheless, most atypical neuroleptics (clozapine, risperidone, olanzapine) can be expected to induce CNS side effects (e.g. anhedonia, lethargy, inability to concentrate and dysphoria) similar in frequency and severity to those observed with standard agents such as butyrophenone and phenothiazines, since they also bind to various neuron receptors (e.g. α_1-adrenergic, H_1-histaminergic and muscarinic receptors) not involved in the antipsychotic activity but instead in the occurrence of adverse effects (Goldberg and Weinberger, 1996; Casey, 1996). Some of these central side effects are difficult to differentiate from the negative symptoms of schizophrenia and may be under-recognised by physicians. They are, however, troublesome in the management of psychotic patients.

In order to avoid the confounding factors that obscure the interpretation of neuropsychological effects of drugs in psychotic patients, central effects of antipsychotics can be investigated in psychometric studies carried out in healthy volunteers, using objec-

tive and subjective tests to compare the actions of the drug with those of placebo on affective, cognitive and psychomotor functions (King, 1990; 1994). The premise underlying such studies is that psychotic patients and healthy volunteers react in similar ways to all drug activities that are pharmacologically unrelated to the antipsychotic effect. Evidence supporting this premise was recently reviewed at a consensus conference convened by the British Association for Psychopharmacology: the conclusion was that properly designed and conducted studies in healthy volunteers are valid for evaluating the side effects of antipsychotic drugs (King and the BAP Consensus Group, 1997).

Results of such studies in non-psychotic volunteers have demonstrated that single oral doses of amisulpride up to 400 mg and multiple daily doses of 50 mg given to young or elderly subjects have minimal and not clinically significant effects on various aspects of psychomotor performance and memory, as well as on subjective evaluations. The studies used tests that assessed the effects of amisulpride on arousal (CFFT), speed of reaction (reaction time), motor activity, vigilance (continuous performance tasks), tracking, information processing, short- and long-term explicit memory, implicit memory (picture stem completion) and procedural memory. Additional studies showed that single doses of amisulpride up to 200 mg do not potentiate the detrimental effects of ethanol or lorazepam.

EEG and cognitive performance evaluations performed in sleep-deprived subjects who were given multiple low doses of amisulpride (50 mg) point to a possible alertness-enhancing effect, as suggested by an increase in absolute (mainly 12–16 Hz and 30–40 Hz) beta and relative fast beta (30–40 Hz) energies on the EEG. Sleep deprivation, which is known to potentiate the sedative effects of drugs, did not reveal any sedative potential of amisulpride; instead, amisulpride reduced the impact on EEG of the vigilance impairment caused by sleep deprivation. The effects of amisulpride were intermediate between those of placebo and caffeine in various psychometric tests. Similar results pointing to the alertness-enhancing effects of a low dose of amisulpride (25 mg or 50 mg) were also reported in previous studies (Grünberger *et al.*, 1989; Saletu *et al.*, 1994).

In a PET scan study performed in both patients with schizophrenia and in normal control subjects, and using labelled bromolisuride as a probe, Martinot *et al.* (1990) estimated the proportion of striatal D_2-receptors blocked by 50–100 mg/day of amisulpride at 4–22%. These data confirm that these doses can be regarded as low compared with the doses used for the treatment of acute psychosis.

On the other hand, repeated administration of a relatively high dose of amisulpride (400 mg daily) demonstrated some sedative effects in various tests, including tracking, reaction time, selective and divided attention and vigilance, in young volunteers. These effects may be ascribed to the drug's non-specific dampening effect on waking arousal, which was subjectively experienced as an unusual drowsiness unaccompanied by dysphoria. However, these effects were significantly less pronounced than those observed after multiple doses of haloperidol 2 mg (Ramaekers *et al.*, 1999).

In contrast to amisulpride, a single dose of 2 mg or 4 mg of haloperidol induced significant deterioration of psychomotor and cognitive skills in young and elderly subjects, as well as a number of mental disturbances, as revealed by alterations of the subjective clinical scale scores. Effects similar in nature but of a larger magnitude were observed after repeated administrations of haloperidol. Comparable results have been found in previous studies. In the literature on haloperidol (Saletu *et al.*, 1983; McClelland *et al.*, 1987; McClelland *et al.*, 1990; Leigh *et al.*, 1992; King, 1993; King, 1994; Hindmarch and Tiplady, 1994; Rammsayer and Gallhofer, 1995; Lynch, *et al.*, 1997), these effects are reported to occur in a dose-dependent manner with doses of haloperidol of 2 mg or higher (King, 1994). There is a high incidence of subjective dysphoria and akathisia after 4 mg and 6 mg of haloperidol in volunteers but not after 2 mg (King *et al.*, 1995). Interestingly, the threshold dose for these effects is very similar to the 'neuroleptic threshold' (3.7 mg) described by McEvoy *et al.* (1991) in schizophrenic patients, suggesting that the ability to tolerate acute doses of neuroleptics may not be markedly different between healthy volunteers and psychotic patients.

Although a 50–300 mg daily dose of amisulpride is effective in the treatment of patients with enduring predominant negative symptoms, positive symptoms in patients with acute exacerbations require daily doses of 400–800 mg or even 1200 mg. Thus the 400 mg dose used in healthy volunteers is at the low end of the therapeutic range for positive symptoms. Controversies remain concerning the dose-dependent effect of haloperidol. In contrast, even though a large range of doses is used in current practice, data have shown that doses of haloperidol as low as 5 mg/day may be realistic for patients who tolerate neuroleptics poorly, usually because of extrapyramidal side effects (Van Putten *et al.*, 1990).

In summary, amisulpride is an atypical antipsychotic that, in contrast to other atypical antipsychotics, binds selectively to D_2/D_3-dopamine receptors with high and similar affinity. In addition, it binds earlier and to a greater extent to mesolimbic neurons, thereby achieving antipsychotic efficacy at cerebral concentrations lower than those causing the degree of striatal receptor occupancy necessary for the emergence of extrapyramidal symptoms. This pharmacological profile, which is also characterised by preferential effects on presynaptic neurones and limbic structures, may explain the clinical efficacy of amisulpride in the treatment of both positive and negative symptoms of schizophrenia and its low propensity to induce extrapyramidal symptoms. The data presented in this review suggest that amisulpride behaves as a well-tolerated antipsychotic drug in healthy volunteers, especially considering the low incidence of extrapyramidal side effects, and the absence of impact on cognitive function. At moderate doses amisulpride is free of sedative effects and moreover at low doses it displays some potential alerting effects. One can expect the side effects of amisulpride to be much less troublesome to patients on chronic antipsychotic treatment than those induced by standard antipsychotics (such as haloperidol) and by the recent atypical antipsychotics that bind to numerous neuron receptors not involved in antipsychotic activity.

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