Enhancement of atomoxetine serum levels by co-administration of paroxetine

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Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood and adolescence. ADHD is characterized by the inability to appropriately modulate attention and/or impulse control and hyperactivity, resulting in social, academic and occupational underachievement. With a prevalence of 3–5%, ADHD is one of the most frequently seen disorders in child and adolescent psychiatry. Medication represents a major component of a multi-modal treatment plan.

Treatment with stimulants is the drug therapy of first choice in ADHD of adulthood. While methylphenidate is mainly used, one third of the patients do not adequately respond to this drug. These patients may profit from a change to treatment with dual active antidepressants.

Atomoxetine is a potent and selective inhibitor of the presynaptic norepinephrine transporter that influences not only norepinephrine but also dopamine concentration. It is used for the treatment of ADHD in children, adolescents and adults. The systemic clearance of atomoxetine involves three oxidative metabolic pathways, whereas the aromatic ring-hydroxylation results in the formation of the primary oxidative metabolite of atomoxetine, 4-hydroxyatomoxetine, which is then glucoronidated and excreted in urine. The formation of 4-hydroxyatomoxetine is mediated by cytochrome P450 (CYP), in particular 2D6 (Sauer et al., 2005).

Variations in plasma atomoxetine exposures can occur because of genetic variation or as a consequence of co-administration with drugs that inhibit CYP2D6. Very recently Michelson et al. (2007) showed significant differences in serum plasma levels of atomoxetine between CYP2D6 extensive metabolizers (EM) and poor metabolizers (PM). Differences in the CYP2D6 genotype and phenotype as well as pharmacokinetic interventions can potentially affect the clinical profile of atomoxetine as seen in efficacy and tolerability of the drug whereas the effect of potent CYP2D6 inhibition on the pharmacokinetics of atomoxetine has rarely been investigated. Belle et al. (2002) showed that paroxetine markedly affects atomoxetine disposition in healthy individuals, resulting in pharmacokinetics similar to that observed in poor metabolizers of CYP2D6 substrates.

Paroxetine is highly metabolized by the liver, resulting in negligible urinary excretion of the intact parent drug (<1%) (DeVane, 2003). Paroxetine undergoes a nonlinear metabolism, steady-state occurs within 8 days and the mean terminal half-life of paroxetine is 18 h which supports a once-daily dosing. The metabolism of paroxetine is largely dependent on the activity of CYP2D6 (Sindrup et al., 1992). The role of paroxetine in clinically significant drug–drug interactions, especially involving metabolic inhibitory effects on the substrates of CYP2D6, has been assessed extensively by a battery of in-vitro studies and clinical pharmacokinetic trials. The recognition of its ability to inhibit CYP2D6 led to a series of studies mostly in healthy volunteers, demonstrating that paroxetine can elevate the plasma concentration of CYP2D6 substrates such as imipramine or desipramine (Alderman et al., 1997; Mitchell, 1997). Despite the demonstration of drug–drug interactions between paroxetine and CYP2D6 substrates in in-vitro studies and in healthy volunteers, there is a marked paucity of reports of clinically significant interactions in psychiatric patients.

We therefore report a case of a 38-yr-old patient suffering from adult ADHD, first diagnosed in November 2006, who was then treated with different doses of atomoxetine before paroxetine was added in order to reach higher serum plasma levels of atomoxetine with the expectation of a better clinical outcome concerning symptoms like attention or impulse control.

Case report

Mr S. is a 38-yr-old male patient suffering from an adult ADHD, first diagnosed at age 38 yr. The patient attended our ADHD consultation hour presenting with prominent listlessness, psychomotoric restlessness, reduced concentration and alertness. This had led to an increase of oversights in his job,
working as a building fitter in a brown-coal strip-
mining operation.

As an outpatient in a psychiatrist’s practice, he was
diagnosed with a major depressive episode and was
treated with duloxetine, a selective norepinephrine
and serotonin reuptake inhibitor. Fortunately, this
produced an improvement in the restlessness but led
to increased tiredness. Therefore, he discontinued the
medication with duloxetine about 8 wk before he was
seen in our consultation hour. Psychopathological
symptoms for the diagnosis of a major depressive
disorder were not evident at the time of exploration.

Neuropsychological testing revealed considerable
deficits in all examined concentration, alertness and
memory tasks as well as in executive functions.
Suppression of inadequate reactions was mostly im-
possible. Using the German version of the Wender
Utah Rating Scale (WURS-k; Retz-Junginger et al.,
2002) it could be shown that the symptoms were
already evident in childhood and Conners’ Adult
ADHD Rating Scales (CAARS) showed noticeable
features in DSM-IV criteria of inattention and impulsivity. Due to additional very imposing impairments
in alertness and concentration a combined type of
an adult ADHD, DSM-IV 314.01, ICD-10 F90.00, was
diagnosed and the patient was treated with atom-
oxetine starting with a single-dose of 40 mg/d, which
was subsequently increased to 40 mg b.i.d. The patient
himself increased the dose as an intuitive attempt
to a three times per day treatment with 30 mg atom-
oxetine as a single dose (cumulative dose 90 mg/d)
reporting a longer lasting effectiveness on psycho-
motor restlessness but no resounding outcome in
alertness and concentration.

Serum atomoxetine levels were measured at three
particular times under two different conditions: first,
30 min after oral administration, second, after 120 min
and finally, 240 min after the intake, using an auto-
mated column-switching method coupled to a HPLC
system and a variable UV detector. In a first inves-
tigation, the atomoxetine plasma concentration was
measured without the addition of paroxetine (base-
line). As the data about the interaction between
paroxetine and atomoxetine metabolism is sparse
and the metabolic effects were unpredictable, we then
added the relatively low dose of 10 mg/d paroxetine
to the treatment regime, and atomoxetine levels were
measured again after reaching the steady state of
paroxetine 14 d later. The baseline assessment re-
vealed serum levels for atomoxetine of 242 ng/ml
after 30 min, 250 ng/ml after 120 min and 111 ng/ml
after 240 min (Figure 1). After co-administration
of paroxetine, atomoxetine serum levels were measured
under otherwise equal conditions. They increased
significantly and were found to be extremely elevated
under all conditions (see Figure 1). Interestingly,
the measured paroxetine levels at the same time-
points were beyond the detection limit of 20 ng/ml
and 5 ng/ml, respectively, as they were measured in
two different laboratories.

Under the treatment regime with paroxetine and
the subsequently higher atomoxetine serum levels, the
patient reported better attention and the ability to fulfil
the requirements of his job much better than before.

Discussion

CYP2D6 has been identified to be the primary enzyme
that is capable of forming 4-hydroxyatomoxetine glu-
curonide as the major metabolite of atomoxetine (Ring
et al., 2002). Concomitant treatment with paroxetine
leads to steady-state pharmacokinetic parameters of
atomoxetine in extensive metabolizers that are similar
to pharmacokinetic values obtained for poor metab-
olizers who were administered atomoxetine alone
(Sauer et al., 2003).

As atomoxetine is a quite new drug which is
seldom prescribed in adults, studies on therapeutic
ranges of plasma concentrations of atomoxetine are
lacking (Baumann et al., 2004) and therapeutic ranges
of plasma concentrations that are considered to be
optimal are not yet proposed.

The reported case shows the role of CYP2D6 in
the biotransformation of atomoxetine and the poten-
tial for other drugs to interact with the metabolism
of atomoxetine and leads to a critical assessment of
the impact of concomitant drug treatment. Co-
administration of paroxetine, a potent inhibitor of
CYP2D6-catalysed reactions, leads to dramatically

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Figure 1. Serum atomoxetine levels: ▲, with the addition of paroxetine; ○, without the addition of paroxetine.
increased serum levels of atomoxetine (twofold 120 min after administration, threefold after 240 min). Our results are consistent with the results of Michelson et al. (2007) who showed that CYP2D6 poor metabolizers taking atomoxetine in doses up to 1.8 mg/kg.d are likely to have greater efficacy, greater increases in cardiovascular tone, and some differences in tolerability compared with CYP2D6 extensive metabolizers taking similar doses.

Although in the presented case, the combination was very well tolerated and adverse effects like increases in heart rate and diastolic blood pressure or treatment-emergent increases to values above normal for ALT, AST, or total bilirubin did not occur, those potential effects must be considered very carefully and need to be checked very critically.

To our knowledge, this is the first single case report that shows significant pharmacokinetic interactions between atomoxetine and paroxetine in a psychiatric patient suffering from adult ADHD reporting dramatically increased serum levels of atomoxetine under co-administration of a CYP2D6-inhibiting agent. The therapeutic treatment regime using the pharmacokinetic interaction between atomoxetine and paroxetine led to a better clinical outcome, improving self-reported attention and reducing oversights in the patient’s job as a building fitter. Our findings lead to the conclusion that large multicentre investigations with standardized drug-monitoring procedures are required to improve our knowledge on correlations between psychopharmaceuticals dosage, serum levels, efficacy and side-effects. CYP polymorphisms should also be analysed in individual cases revealing metabolic abnormalities contributing to a better clinical outcome.

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Statement of Interest
None.

References


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