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LETTER TO THE EDITOR

Inhibition of CYP2D6 with low dose (5 mg) paroxetine in patients with high 10-hydroxynortriptyline serum levels – a review of routine practice

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Tables of Links

TARGETS
Enzymes [2]
Cyp2D6

LIGANDS
Nortriptyline
Paroxetine

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Nortriptyline, a tricyclic antidepressant (TCA) with selective noradrenergic reuptake inhibitor and little anticholinergic characteristics, is metabolized by CYP2D6 to active metabolites, E-10-hydroxy(OH-)nortriptyline and Z-10-hydroxy(OH-)nortriptyline. Severe depression and depression with psychotic features in the elderly are treated with TCAs. Nortriptyline is preferred in the Netherlands, because it causes the least adverse drug reactions [3]. The therapeutic range of nortriptyline serum levels for anti-depressive treatment lies between 50 μg l^{-1} and 150 μg l^{-1} [4]. The 10-OH-nortriptyline serum level is preferably kept below 200 μg l^{-1} as higher levels are associated with increased occurrence of side effects (e.g. increase in QRS duration and Q-Tc intervals) [5]. So far, only one prospective pharmacokinetic study in five healthy volunteering ultra-rapid metabolizers has been published describing the effects of the addition of 10–20 mg paroxetine (for CYP2D6 inhibition) to 50 mg nortriptyline in order to phenoconvert ultra-rapid metabolizers into poor metabolizers [6]. In the Reinier van Arkelgroep (RvA), 's-Hertogenbosch, the Netherlands, a mental health institution, the addition of low dose (5 mg) paroxetine once daily to patients with high 10-OH-nortriptyline (above 200 μg l^{-1}) serum levels is applied *ad hoc* to carefully lower the 10-OH-nortripyline level and maintain patients on nortriptyline therapy. The aim of this review of routine practice was to retrospectively assess the pharmacokinetic impact of this once daily 5 mg paroxetine addition on nortriptyline and 10-OH-nortriptyline serum levels in patients with high 10-OH-nortriptyline serum levels.

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Patients treated with nortriptyline in the RvA between 1 July 2011 and 1 July 2015 were considered; patients with at least one high 10-OH-nortriptyline serum level and to whom paroxetine 5 mg was precribed for phenoconversion are described. Patients with co-medication that influences CYP2D6 activity (such as bupropion, cinacalcet, fluoxetine, quinidine, duloxetine, sertraline, terbinafine, amiodarone, cimetidine, dexamethasone, rifampin [7]) were disregarded. Nortriptyline and unconjugated 10-OH-nortriptyline were measured in serum by high-performance liquid chromatography with photodiode array detection. To assess the impact of paroxetine on nortriptyline metabolism, the last nortriptyline and 10-OH-nortriptyline serum levels before, and the first nortriptyline and 10-OH-nortriptyline serum levels after reaching the steady state situation, which is one week after start of paroxetine, were evaluated.

Four patients received 5 mg paroxetine for phenoconversion. Before the start of paroxetine administration, three patients had nortriptyline serum levels in the therapeutic range and one patient had a nortriptyline serum level below the therapeutic range. All patients had 10-OH-nortriptyline serum levels above 200 μg l^{-1}. After the addition of 5 mg paroxetine, all subsequent nortriptyline serum levels fell within the therapeutic range and three out of four of the subsequent 10-OH-nortriptyline serum levels decreased to below 200 μg l^{-1}. The effect of the low dose paroxetine on nortriptyline and 10-OH-nortriptyline serum levels are summarized in Table 1 and shown in Figure 1.

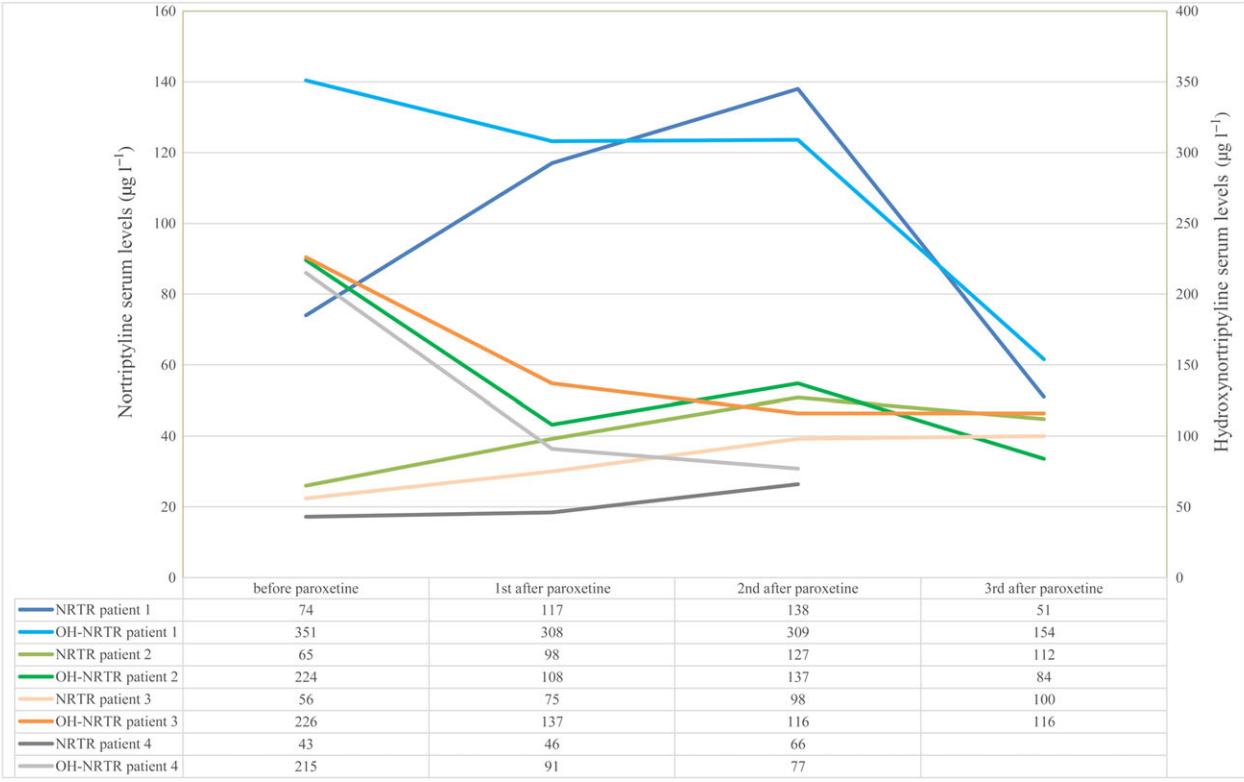
This study suggests that the addition of low dose (5 mg) paroxetine to nortriptyline treatment is able to slow down nortriptyline metabolism. The increase in the ratio between nortriptyline/hydroxynortriptyline serum levels after the addition of paroxetine in all patients supports this. The outcomes are comparable with previous research which showed a decrease of 40% in 10-OH-nortriptyline serum levels after addition of paroxetine [6]. However, the retrospective design does have limitations; for example, the relatively small decrease of 10-OH-nortriptyline serum level in patient 1 could not be explained with the retrieved data.

The intentional introduction of a drug–drug interaction to normalize skewed drug metabolism to optimize drug use is well known. Addition of allopurinol to thiopurine use in patients with high thiopurine methyltransferase activity and the addition of ritonavir to lopinavir use are both comparable interventions that are included in standard care [8, 9]. No adverse drug reactions and changes in tolerability are recorded during the addition, and although both paroxetine and nortriptyline inhibit serotonine reuptake, none of the patients reported signs of serotonine syndrome which would be a possible adverse drug interaction. However, the dose of paroxetine is so low that despite the complex metabolism of this drug, with autoinhibition, the 5 mg once daily dosage will not lead to high paroxetine levels or CYP2D6 saturation [6]. According to the outcomes of this study, the addition of 5 mg paroxetine lowers 10-OH-nortriptyline serum levels and may make treatment with nortriptyline possible for patients who have few other treatment options. To further adress these possibilities, the research will be continued in a prospective design.

Table 1

Impact of 5 mg paroxetine on nortriptyline serum levels and hydroxy(OH)-nortriptyline serum levels in four patients

Pt	F/M	Age (years)	Nortriptyline once daily dose (mg)	Nortriptyline serum levels before (μg l^{-1})	OH-nortriptyline serum levels before (μg l^{-1})	Nortriptyline serum levels after (μg l^{-1})	OH- nortriptyline serum levels after (μg l^{-1})	% decrease in OH- nortriptyline serum levels	% increase in nortriptyline serum levels	Before paroxetine Nortriptyline/ OH-nortriptyline	After paroxetine Nortriptyline/ OH-nortriptyline
1	F	74	75	74	351	117	308	12%	58%	0.2	0.37
2	F	83	50	65	224	98	109	51%	51%	0.29	0.89
3	F	44	100	56	226	75	137	39%	34%	0.24	0.54
4	F	68	50	43	215	66	77	64%	53%	0.2	0.85
Averages (± s.d.)		67.25 ± 16.7		59.5 ± 13.2	254 ± 64.8	89 ± 23.0	157.8 ± 103.1	41.5% ± 22%	49% ± 10%	0.23 ± 0.04	0.66 ± 0.25



	before paroxetine	1st after paroxetine	2nd after paroxetine	3rd after paroxetine
NRTR patient 1	74	117	138	51
OH-NRTR patient 1	351	308	309	154
NRTR patient 2	65	98	127	112
OH-NRTR patient 2	224	108	137	84
NRTR patient 3	56	75	98	100
OH-NRTR patient 3	226	137	116	116
NRTR patient 4	43	46	66	
OH-NRTR patient 4	215	91	77	

Figure 1

Increase of nortriptyline and decrease of hydroxynortriptyline serum levels (μg l^{-1}) after the addition of 5 mg paroxetine to the four patients. (Patient 1 had a dose reduction from once daily 75 mg to once daily 40 mg after the second follow-up nortriptyline/OH-nortriptyline serum level)

Competing Interests

There are no competing interests to declare.

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