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SHORT REPORT

Inhibition of CYP2D6 with low dose (5 mg) paroxetine in patients with high 10-hydroxynortriptyline serum levels-A prospective pharmacokinetic study

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The antidepressant nortriptyline is metabolized by cytochrome P450 2D6 (CYP2D6) to the less active and more cardiotoxic drug metabolite, 10-hydroxynortriptyline. High serum levels of this metabolite (>200 μg/L) may lead to withdrawal of nortriptyline therapy. Adding CYP2D6 inhibitors reduce the metabolic activity of CYP2D6 (phenoconversion) and so decrease the forming of hydroxynortriptyline. In this study, 5 mg paroxetine is administered to patients with high hydroxynortriptyline concentrations (>200 μg/L). The shift in number of patients to therapeutic nortriptyline (50–150 μg/L) and safe hydroxynortriptyline (<200 μg/L) concentrations, and the degree of phenoconversion, expressed as the change in ratio nortriptyline/hydroxynortriptyline concentrations before and after paroxetine addition, are prospectively observed and described. After paroxetine addition, 12 patients (80%) had therapeutic nortriptyline and safe hydroxynortriptyline concentrations. Hydroxynortriptyline concentrations decreased in all patients. The average nortriptyline/hydroxynortriptyline concentrations ratio increased from 0.32 to 0.59. This study shows that 5 mg paroxetine addition is able to lower high hydroxynortriptyline serum levels to safe ranges.

KEYWORDS
CYP2D6, hydroxynortriptyline, nortriptyline, paroxetine addition, phenoconversion

1 | INTRODUCTION

Tricyclic antidepressants (TCAs) are important options for the treatment of severe depression and depression with psychotic features. Nortriptyline, a selective noradrenergic reuptake inhibitor, is the preferred TCA for elderly in the Netherlands because of its favourable adverse drug reaction (ADR) profile compared to other TCAs.[1] Nortriptyline is metabolized by cytochrome P450 isoenzyme 2D6 (CYP2D6) to the less active and more cardiotoxic drug metabolite, 10-hydroxynortriptyline.[2]

Nortriptyline serum levels should be kept in the therapeutic range (50–150 μg/L) and E-10-hydroxynortriptyline serum levels must be in the safe range (<200 μg/L) as higher levels are associated with cardiotoxicity.[3] Genetic polymorphisms of CYP2D6 can significantly influence the efficacy and safety of nortriptyline. Ultrarapid CYP2D6 metabolizers may have higher levels of the metabolite hydroxynortriptyline and are prone to ADRs, therapeutic failures and withdrawal of their treatment.[4] Reducing the metabolic activity of CYP2D6, phenoconversion, with CYP2D6 inhibitors such

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as paroxetine could be an effective strategy for rapid metabolizers to keep nortriptyline and hydroxynortriptyline serum levels within preferable ranges.[5] So far, there are only 2 published studies of this intended drug–drug interaction, both with a very small number of participants. One is a prospective pharmacokinetic study in 5 healthy volunteering ultrarapid metabolizers and the other is a retrospective review of routine practice (case-series) conducted in 4 female patients using nortriptyline, all with high E-10-hydroxynortriptyline serum levels above 200 μg/L.[5,6] Considering the addition of 5 mg paroxetine in patients with high hydroxynortriptyline serum levels belongs to standard care in in the mental health institute, Reinier van Arkel,'s-Hertogenbosch, the Netherlands. The aim of this research was to prospectively observe the effects of adding paroxetine to nortriptyline therapy on nortriptyline and hydroxynortriptyline serum levels in patients with high (>200 μg/L) hydroxynortriptyline concentrations.

What is already known about this topic

- In CYP2D6 ultrarapid metabolizers using nortriptyline, hydroxynortriptyline serum levels are often too high leading to toxicity while nortriptyline serum levels may be too low for efficacy.

What this study adds

- This pharmacokinetic study shows that the addition of a low dose of paroxetine (5 mg) to inhibit CYP2D6 metabolic activity in patients using nortriptyline, who have high hydroxynortriptyline serum levels, decreases hydroxynortriptyline serum levels to safe ranges and increases low nortriptyline serum levels to therapeutic levels.

2 | METHODS

An observational prospective pharmacokinetic study was conducted between September 2016 and September 2019 in patients treated with nortriptyline and low dose, 5 mg, paroxetine addition within the mental health institute Reinier van Arkel,'s-Hertogenbosch, the Netherlands. The study received a waiver for the Dutch Medical Research Involving Human Subjects Act (WMO) by the regional medical ethics committee Brabant (#NW2016–05).

Patients were selected if they were treated with nortriptyline and had at least 1 high hydroxynortriptyline serum level (above 200 μg/L) for which paroxetine 5 mg once daily was prescribed. Exclusion criteria were: comedication that influences CYP2D6 activity as defined by Flockhart[7] and renal function disorders defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2.[8] Eligible patients were asked informed consent to participate in the study. For all participating patients, the last nortriptyline serum level before paroxetine addition and the first hydroxynortriptyline serum level within 1 to 4 weeks after paroxetine addition, were collected.

Nortriptyline and E-10-hydroxynortriptyline were measured in serum by high-performance liquid chromatography with photodiode array detection in the laboratory of the Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands.

The following information in the electronic health record was collected: nortriptyline dose before and with paroxetine addition, and concomitant drugs that interact via CYP2D6.[7]

We calculated the prevalence of patients with both nortriptyline therapeutic serum levels (50–150 μg/L) and safe hydroxynortriptyline (<200 μg/L) serum levels after paroxetine addition.

The impact of paroxetine addition for all observed patients is expressed by the decrease in hydroxynortriptyline serum levels (range, average, %). The change in metabolic activity, phenoconversion, is expressed as the change in ratio nortriptyline/hydroxynortriptyline serum levels before and after the addition of paroxetine.

2.1 | Statistical analysis

Since serum levels of nortriptyline and hydroxynortriptyline are not normally distributed, non-parametric tests are used for statistical analysis. A *P*-value <.05 was considered statistically significant.

3 | RESULTS

A total of 17 patients received 5 mg paroxetine per day for phenoconverting nortriptyline metabolism by CYP2D6 inhibition. One patient stopped because of experiencing an increase in depressed mood. Another patient was excluded because nortriptyline and hydroxynortriptyline serum levels were not measured between 1 and 4 weeks after 5 mg paroxetine addition. The effects of addition of 5 mg paroxetine on hydroxynortriptyline and nortriptyline serum levels in the 15 remaining patients are summarized in Table 1.

3.1 | Overall effect of 5 mg paroxetine addition on hydroxynortriptyline and nortriptyline serum levels

Before paroxetine addition, hydroxynortriptyline serum levels of the 15 observed patients ranged from 204 to 407 μg/L (average 264 μg/L) and 2 of these patients had nortriptyline serum levels below the therapeutic range. After paroxetine 5 mg addition, 12 out of 15 patients (80.0%) had nortriptyline and hydroxynortriptyline serum levels within the preferred ranges. Hydroxynortriptyline serum levels decreased in all patients (ranging now from 96 to 270 μg/L, average 173.0 μg/L) and 13 patients reached hydroxynortriptyline serum levels below 200 μg/L. One patient (patient 14) with a low

TABLE 1 Impact of 5 mg paroxetine once daily on nortriptyline and hydroxynortriptyline (OH-nortriptyline) serum levels. Therapeutic nortriptyline serum levels: 50–150 μg/L, safe OH-nortriptyline serum levels: <200 μg/L

Patient	F/M	Age (y)	Nortriptyline dose before (mg)	Nortriptyline dose with paroxetine addition (mg)	Nortriptyline serum level before (μg/L)	Nortriptyline serum level after (μg/L)	OH-nortriptyline serum level before (μg/L)	OH-nortriptyline serum level after (μg/L)	Ratio paroxetine nortriptyline/OH-nortriptyline before	Ratio paroxetine nortriptyline/OH-nortriptyline after
Patients without nortriptyline dose changing										
1	F	68	50	50	41	106	215	182	0.19	0.58
2	F	65	100	100	64	87	204	186	0.31	0.47
3	F	45	125	125	120	121	226	169	0.53	0.72
4	F	54	250	250	86	142	240	206	0.36	0.69
5	M	54	100	100	141	67	361	270	0.39	0.25
6	F	80	50	50	75	96	230	188	0.33	0.51
7	F	71	100	100	78	121	261	199	0.30	0.61
8	F	80	75	75	100	130	297	184	0.34	0.71
9	F	75	75	75	86	78	221	96	0.39	0.81
Patients with concomitant nortriptyline dose changes										
Patients with nortriptyline dose increase										
10	M	72	75	175	97	115	246	183	0.39	0.63
11	M	65	50	100	112	149	276	178	0.41	0.84
Patients with nortriptyline dose decrease										
12	F	73	75	50	58	92	221	151	0.26	0.61
13	F	73	100	50	70	58	407	110	0.17	0.53
14	F	46	150	100	36	33	280	154	0.13	0.21
15	M	68	100	75	93	103	277	139	0.34	0.74
Average (± s.d.)		66.8 ± 11.4	98.3 ± 50.4	98.3 ± 53.8	83.8 ± 28.5	99.9 ± 33.0	264.1 ± 56.5	173.0 ± 45.4	0.32 ± 0.1	0.59 ± 0.18

nortriptyline serum level before paroxetine addition, kept nortriptyline serum levels below the therapeutic range.

The impact of paroxetine on CYP2D6 metabolic activity is further showed by the increase in average nortriptyline/hydroxynortriptyline serum level ratio from 0.32 to 0.59 ($P < .01$), which expresses the introduced phenoconversion even more.

3.2 | Effect of 5 mg paroxetine addition on nortriptyline and hydroxynortriptyline serum levels for patients without nortriptyline dose changes

Nine patients had no changes in their nortriptyline dose. Their average hydroxynortriptyline serum level decreased with 25.5% from 250.6 to 186.7 μg/L and their average nortriptyline serum level increased with 19.8% from 87.9 to 105.3 μg/L. Seven out of 9 patients reached hydroxynortriptyline serum levels <200 μg/L. All patients kept or reached therapeutic nortriptyline serum levels.

4 | DISCUSSION

This study shows that adding low dose (5 mg) paroxetine to nortriptyline treatment in patients with high hydroxynortriptyline serum levels is able to attain safe hydroxynortriptyline and therapeutic nortriptyline serum levels. This outcome is in line with a previously published case series of this addition in 4 patients of whom 3 reached preferred serum levels for both nortriptyline and hydroxynortriptyline.[5]

Adding a new drug with possible ADRs should always be carefully considered. Although ADRs are not specifically researched in this study, it is not expected that the low dose (5 mg) paroxetine once daily will lead to substantial ADRs, to high paroxetine levels or to CYP2D6 saturation.[9]

A limitation of this pharmacokinetic study is the observational design and there were no measures to improve adherence to the intended treatment and prescribed medication. The changes in serum drug and metabolite levels of Patient 5, for example, are not consistent with changes in other patients and not with what is expected. Furthermore, the nortriptyline dose was not fixed and prescribers were free to adjust the nortriptyline dose to what they expected best for their patients. Although, Patient 14 had low nortriptyline serum levels before paroxetine addition, the nortriptyline dose was reduced and, in this case, paroxetine addition was not able to increase the nortriptyline serum level to therapeutic ranges. In this study, the subpopulations of patients with nortriptyline dose unchanged, increased and decreased with paroxetine addition are too small to draw conclusions on advice for nortriptyline dosing when adding paroxetine 5 mg. Further research on nortriptyline dosing with paroxetine addition should be conducted.

Despite the rather small number of patients, this study shows that paroxetine addition to nortriptyline therapy in patients with high hydroxynortriptyline serum levels as a result of high CYP2D6 metabolic activity, such as in CYP2D6 ultrarapid metabolizers, allows for the attainment of safe hydroxynortriptyline serum levels.

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The authors have no competing interests to declare.

CONTRIBUTORS

N.T. Jessurun wrote the manuscript with input from all other authors. N.T. Jessurun, E.P. van Puijenbroek, R.J. van Marum, K. Grootens, H.J. Derijks contributed to the research design, N.T. Jessurun, A.M.A. Vermeulen Windsant-van den Tweel, O. Mikes performed the research and analysed the data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Richtlijnontwikkeling LsM. Addendum Ouderen bij de Multidisciplinaire Richtlijn Depressie 2008. www.ggzrichtlijnen.nl/richtlijn/doc/download.php?id=62%bijlage=1. Accessed June 7, 2016.
2. Nordin C, Bertilsson L. Active hydroxymetabolites of antidepressants. Emphasis on E-10-hydroxy-nortriptyline. *Clin Pharmacokinet*. 1995;28(1):26-40.
3. Schneider LS, Cooper TB, Severson JA, Zemplenyi T, Sloane RB. Electrocardiographic changes with nortriptyline and 10-hydroxynortriptyline in elderly depressed outpatients. *J Clin Psychopharmacol*. 1988;8(6):402-408.
4. Chaudhry SR, Muhammad S, Eidens M, et al. Pharmacogenetic prediction of individual variability in drug response based on CYP2D6, CYP2C9 and CYP2C19 genetic polymorphisms. *Curr Drug Metab*. 2014;15(7):711-718.
5. Jessurun N, van Puijenbroek EP, Otten LS, et al. Inhibition of CYP2D6 with low dose (5 mg) paroxetine in patients with high 10-hydroxynortriptyline serum levels - a review of routine practice. *Br J Clin Pharmacol*. 2017;83(5):1149-1151.
6. Laine K, Tybring G, Hartter S, et al. Inhibition of cytochrome P4502D6 activity with paroxetine normalizes the ultrarapid metabolizer phenotype as measured by nortriptyline pharmacokinetics and the debrisoquin test. *Clin Pharmacol Ther*. 2001;70(4):327-335.
7. Flockhart DA. Cytochrome P450 Drug Interaction Table 2007. https://drug-interactions.medicine.iu.edu. Accessed August 13, 2019.
8. Schneider LS, Cooper TB, Suckow RF, et al. Relationship of hydroxynortriptyline to nortriptyline concentration and creatinine clearance in depressed elderly outpatients. *J Clin Psychopharmacol*. 1990;10(5):333-337.
9. Leucht S, Hackl HJ, Steimer W, Angersbach D, Zimmer R. Effect of adjunctive paroxetine on serum levels and side-effects of tricyclic antidepressants in depressive inpatients. *Psychopharmacology (Berl)*. 2000;147(4):378-383.

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