

# Clozapine plasma levels in patients switched from clozapine liquid to tablets

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**AIM** • To compare clozapine plasma levels in patients switched from clozapine liquid to clozapine tablets.

**DESIGN** • Retrospective, paired comparisons of plasma level/dose ratios in patients prescribed clozapine liquid and then clozapine tablets in a naturalistic setting.

**SUBJECTS AND SETTINGS** • 10 inpatients from the Maudsley and Bethlem hospitals in South London.

**OUTCOME MEASURES** • Mean clozapine dose, mean plasma level and mean plasma level/dose ratio.

**RESULTS** • Patients who received a mean dose of clozapine liquid of 530mg/day showed a mean plasma level of 329µg/L (ratio=0.636). After being switched to a mean dose of 580mg/day in tablet form, plasma levels averaged 629µg/L (ratio=1.042;  $P=0.047$ ). This change in plasma levels could not be accounted for by the change in dose or by drug interaction.

**CONCLUSIONS** • Clozapine liquid appears to afford lower clozapine plasma levels than clozapine tablets, perhaps because of reduced bioavailability. The utility of this preparation is therefore somewhat limited. Care is needed when switching from clozapine liquid to clozapine tablets.

Clozapine is an atypical antipsychotic used in patients who are unresponsive, or in some way intolerant, to other antipsychotic drugs. Its efficacy in refractory schizophrenia was first demonstrated by Kane *et al.*<sup>1</sup> Today, it is still the drug of choice in refractory schizophrenia.<sup>2</sup> This is because, despite early hopes, other atypicals have largely been found not to be effective in this condition.<sup>3</sup>

Clozapine is available commercially only in tablet form (25mg and 100mg). However, there are some patients who find it difficult to swallow tablets and there are those in whom compliance cannot be assured despite close supervision. An extemporaneous preparation of clozapine liquid (clozapine 100mg tablets suspended in Guy's hospital paediatric base) was formulated by Ramuth *et al.*<sup>4</sup> however pharmaco-

kinetic parameters of the preparation were not studied. The preparation was found to be suitable for hospital use.<sup>4</sup>

In our trust, clozapine liquid suspension is frequently prescribed for patients who it is thought may attempt not to take medicine administered to them. On several occasions, however, it had been noted that clozapine plasma levels were unexpectedly low in patients receiving and taking clozapine liquid. We undertook to examine this phenomenon in a retrospective comparison of plasma levels in patients receiving clozapine liquid and then clozapine tablets.

## METHOD

Using the Clozaril Patient Monitoring Service, patients on clozapine at the Maudsley and Bethlem Royal hospitals were identified. From this, and using dispensing

records, patients who had in the past three years been switched from clozapine suspension to clozapine tablets were identified.

Patient notes, current and past prescription charts, medical records and clozapine dispensing records at both hospitals were used to obtain the necessary information.

Clozapine plasma level assay results were obtained from the medical toxicology unit, Guy's and St Thomas' Hospital trust. Plasma levels were assayed using high performance liquid chromatographic analysis<sup>4</sup> of trough (pre-dose) samples.

## RESULTS

Ten patients were identified who had been switched from clozapine liquid to clozapine tablets. The results are shown in Table 1.

Graph 1 shows the mean dose and mean clozapine levels before and after switching from liquid to tablets. The difference between mean ratios before and after switching (0.636 vs 1.042) was statistically significant ( $P=0.047$ ; two-tailed paired *t*-test).

Samples were taken on average (medians) 15 days before switching from liquid to tablets (range 1–178 days) and 16 days afterwards (range 5–48 days).

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**TABLE 1: TOTAL DAILY DOSE, CLOZAPINE LEVEL AND DOSE/LEVEL RATIOS BEFORE AND AFTER SWITCHING FROM CLOZAPINE LIQUID TO TABLETS**

Patient ID	Liquid			Tablets		
	Total daily dose (mg)	Level (µg/L)	Ratios (level/dose)	Total daily dose (mg)	Level (µg/L)	Ratios (level/dose)
1	250	110	0.440	300	150	0.500
2	400	540	1.350	800	1050	1.313
3	700	460	0.657	700	670	0.957
4	600	190	0.317	600	490	0.817
5	600	290	0.483	600	290	0.483
6	600	360	0.600	600	370	0.617
7	500	20	0.040	550	730	1.327
8	400	460	1.150	400	430	1.075
9	550	230	0.418	550	810	1.473
10	700	630	0.900	700	1300	1.857
Mean	530	329	0.636	580	629	1.042

TABLE 2: SMOKING HABITS AND CONCOMITANT DRUGS BEFORE AND AFTER SWITCHING FROM CLOZAPINE LIQUID TO TABLETS

Patient ID	Smoker at time of pre-switch level (Y/N)	Concomitant drugs at the time of pre-switch level (total daily dose)	Smoker at time of post-switch level (Y/N)	Concomitant drugs at the time of post-switch level (total daily dose)	Comments
1	Y	Trifluoperazine 10mg (patient known to misuse cocaine and cannabis)	Y	Trifluoperazine 10mg Procyclidine 10mg (patient known to misuse cocaine and cannabis)	No change in therapy. Not known to interact
2	Y	Lithium 800mg Clonazepam 4mg	Y	Lithium 800mg	Not known to interact
3	Y	Sodium valproate 1,200mg	Y	Sodium valproate 1,500mg Clonazepam 1mg	Sodium valproate may increase clozapine levels. Small increase in valproate dose may give rise to further increase clozapine levels
4	Y	Sodium valproate 2,400mg Omeprazole 20mg Lactulose 20ml Amisulpride 400mg	Y	Sodium valproate 2,400mg Omeprazole 40mg Lactulose 20ml Amisulpride 400mg	No change in sodium valproate use or dose. Other drugs not known to interact
5	Y	Metformin 2,000mg Haloperidol 20mg Hyoscine 1,200µg Sodium valproate 1,000mg Gliclazide 160mg (patient known to misuse cannabis)	Y	Metformin 2,000mg Haloperidol 20mg Hyoscine 1,200µg Erythromycin 1,000mg Gliclazide 160mg (patient known to misuse cannabis)	Removal of sodium valproate likely to result in a reduction in clozapine levels Erythromycin may increase clozapine plasma levels Other drugs not known to interact
6	Y	Haloperidol 2mg Citalopram 40mg Lorazepam 4mg	Y	Haloperidol 2mg Citalopram 40mg Lorazepam 4mg	None of these drugs is known to interact with clozapine
7	Y	Amisulpride 50mg	Y	Clonazepam 8mg Hyoscine 900µg	None of these drugs is known to interact with clozapine
8	Y	Sodium valproate 2,000mg Hyoscine 300µg Lactulose 20ml Diazepam 5mg	Y	Sodium valproate 2,000mg Lactulose 10ml Pirenzepine 50mg	Sodium valproate may increase clozapine plasma levels but no change in dose or use Other drugs not known to interact
9	Y	Fluoxetine 40mg	Y	Fluoxetine 40mg	Fluoxetine increases clozapine plasma levels but no change in use or dose
10	Y	Sodium valproate Chrono 900mg  Clonazepam 1.5mg Ferrous sulphate 400mg Co-dydramol 6 tablets in 24 hours	Y	Sodium valproate Chrono 900mg  Clonazepam 1.5mg Ferrous sulphate 400mg Co-dydramol 6 tablets in 24 hours	Sodium valproate may increase clozapine levels but no change in use or dose. Other drugs not known to interact

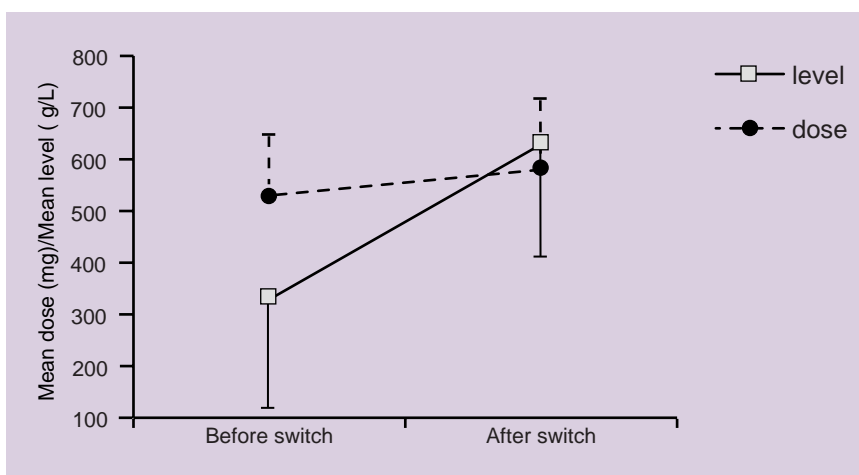


Figure 1: Mean dose and mean clozapine levels before and after switching (error bars show one standard deviation from mean)

## DISCUSSION

In this study clozapine plasma levels increased significantly when patients prescribed clozapine liquid were switched to clozapine tablets. The mean plasma level for patients taking clozapine liquid was 329µg/L and this increased to 629µg/L

when taking clozapine tablets (the mean dose increase was only 50mg: 530mg to 580mg/day).

The main strength of this study is that each patient received both liquid and tablet forms of clozapine, thus controlling for many subject characteristics. We accounted for changes in dosage by calculating and

comparing dose/level ratios (Table 1). We also recorded co-prescribed medication both before and after switching from liquid to tablets in an attempt to rule out plasma level changes brought about by interacting drugs (Table 2). Of the 10 patients studied, all smoked before and after the switch (smoking reduces clozapine plasma levels<sup>5</sup>), and in four patients no interaction was suspected at any time. Of the remaining six patients prescribed concurrent drugs known to interact<sup>6</sup> four saw no change in the prescribing of these drugs during the period assessed. Thus, only for two subjects were pharmacokinetic interactions likely to confound our findings. Patient 3 was prescribed a higher dose (1,500mg/day versus 1,200mg/day) of valproate while on clozapine tablets than when receiving liquid clozapine. Since valproate has been reported to inhibit clozapine metabolism, it is possible that this increase in dosage may have engendered a rise in clozapine level. Patient 5 was prescribed valproate while on liquid clozapine but not while prescribed clozapine tablets. However, erythromycin was prescribed while on clozapine tablets but not while on liquid. Both valproate and erythromycin inhibit clozapine metabolism and so increase plasma levels, but it is not

possible to estimate the overall effect of the changes in prescribing on clozapine plasma levels in this case.

Given these observations, it seems probable that the change in clozapine plasma levels observed occurred as a result of the switch from liquid to tablet form. It is possible that patients were receiving, inadvertently, an incorrect dose of clozapine while prescribed the liquid form, perhaps through decay of substance or through erroneous administration of inadequately shaken suspension. It is also possible that patients were less compliant with liquid than with tablets.

While these possibilities cannot be discounted, it is noteworthy that on previous occasions we have asked for assays to be performed on part-used containers of clozapine liquid and found the measured concentration to be within 5 per cent of the stated amount. By the time of this study, we had discounted as a possibility decay of clozapine in liquid form and had taken steps to ensure accurate dosing with the liquid form (by requiring nursing staff to invert bottles and to shake them for at least a minute). In addition, in all cases where poor compliance was suspected, patients were closely observed by nursing staff for at least half an hour after administration of liquid to ensure that the liquid had been swallowed and retained.

This study did not examine reasons why clozapine plasma levels might be relatively lower following administration in liquid form. It is possible that clozapine is better absorbed in tablet form. It is also possible that the use of trough plasma samples did not reflect accurately plasma levels during dosing intervals: peak plasma levels obtained from the liquid form would be expected to occur earlier and be higher than with tablets. However, clozapine has a plasma half life of up to

14 hours in long-term treatment<sup>7</sup> and all of the subjects here were receiving clozapine twice or three times daily. It seems unlikely therefore that the differences in trough levels observed here were simply a result of more abrupt absorption and apparently more rapid removal of clozapine given in liquid form. However, changes in absorption characteristics are thought to be responsible for relapses seen in patients switched from one brand of clozapine tablets to another.<sup>8</sup>

These results bring into question the usefulness of clozapine liquid. Should it still be used when it is known that tablets give higher plasma levels? Perhaps the most important observation to make in this respect is that of our experience in patients switched from tablets to liquid. We frequently see patients prescribed clozapine in tablet form who have plasma levels close to zero. When

switched to liquid, plasma levels rise substantially within days. It is clear therefore that liquid clozapine still represents an essential option in covert or suspected non-compliance. However, considerable caution is required when switching from liquid to tablets — patients should be closely monitored and plasma level measurements performed.

In conclusion, this study has demonstrated that in patients switched from clozapine liquid to clozapine tablets, clozapine plasma levels rise substantially. Clozapine liquid remains a helpful remedy for covert non-compliance but further research is needed to establish the pharmacokinetic profile of this formulation.

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