Literature Values of Terminal Half-Lives of Clozapine are Dependent on the Time of the Last Data Point

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Dear Editor,

During a pharmacokinetic study involving clozapine, we noticed different terminal half-lives for clozapine when the time of the last data point was changed. To validate this notion, a systematic literature search was conducted in PubMed and Google Scholar for the terminal half-life values of clozapine in humans. Twenty-one publications were identified to contain terminal half-life information of clozapine when it was administered alone (Table 1). The average literature values of the terminal half-lives of clozapine were calculated to be 10.2, 13.2, 14.2, 18.3 and 29.2 hours with a last data point at 12, 24, 48, 72 and 120 hours, respectively (Table 1). Thus, there is a trend to find a longer terminal half-life when longer blood sampling times are used in pharmacokinetic studies on clozapine in humans.

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Table 1. Literature values of terminal half-lives of clozapine in humans with different times for the last data point

Time of last data point					
12h	**24h**	**48h**	**72h**	**120h**	
					References
15.8					(11)
	10.3				(12)
			14.1		(13)
		8.2			(13)
	13.3				(14)
			13.7		(15)
7.6					(16)
	17.3				(17)
		15.5			(18)
		18.6			(19)
10.5					(20)
				28	(21)
			27.7		(22)
7.0					(23)
			17.6		(24)
		14.3			(25)
9.0					(26)
				30.4	(27)
10.6					(28)
	12[a]				(29)
		14.5			(30)
11.0[b]					(31)
Mean half-life values					
10.2	**13.2**	**14.2**	**18.3**	**29.2**	

[a] Half-life values estimated from graph in the publication.
[b] average half-life values when two clozapine products were investigated.

Clozapine treatment is effective in 30% to 38% of treatment-resistant schizophrenic patients (1). Many pharmacokinetic studies and case reports have been published on clozapine because clozapine has a narrow therapeutic window and increased plasma concentrations of clozapine can lead to serious side effects such as toxic delirium and sedation (2) or convulsions (at plasma concentrations above 1300 ng/ml) (3).

A one compartment model is often assumed in calculating the half-lives of therapeutic agents because the differences are important only if the fraction of the dose lingering at the end of a dose interval is substantial so that it can influence the steady-state concentrations. However, differences in reported half-life values may influence clinical decisions on dose regimens of clozapine. This matter could be further complicated by the numerous drug-drug interactions reported during its clinical use (4-6). Most of these interactions are due to inhibition or induction of cytochrome P450 enzymes responsible for the metabolism of clozapine (7-9). It is however worth noting the relatively small differences in half-lives when the last data points were 12, 24 and 48 hours.

"Terminal half-lives" of therapeutic agent are routinely computed and reported in the literature. However, terminal half-lives are constant only when there is a clear log-linear phase. Thus, for drugs with a third deep compartment such as clozapine, one should remember to consider the time of the last data point when comparing the terminal half-life. Similar cases may also exist in the literature for other therapeutical agents (10).

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