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Short Communication

Plasma concentrations of chlorpromazine and blood collection method

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Introduction

Methods of sample collection are a source of systematic variation in plasma measurements of a variety of drugs [1–7] including psychotropics [8–11]. Plasma concentrations of chlorpromazine (CPZ) have been measured recently in patients treated with CPZ [12–16]. The contribution of different methods of sample collection to the determination of CPZ in plasma was therefore assessed in a clinical setting.

Experimental

The subjects were twenty-one psychiatric inpatients who had been receiving stable oral doses of CPZ for at least one week. The patients gave informed consent.

Heparinized venous blood samples were obtained simultaneously using Vacutainer (Becton Dickinson) and Venoject (Kimble Terumo) tubes. Samples were collected 11–15 h after the last oral dose. Plasma was separated immediately by centrifugation. Duplicate aliquots were prepared from each pair of plasma samples; these were frozen at −70°C prior to analysis.

Plasma CPZ was assayed by gas chromatography–mass spectrometry using a modification of the method of Alfredsson *et al.* [13] as previously described [17]. Analyses were performed in duplicate; results agreed within 5% and mean values were calculated.

Results and Discussion

Concentrations of CPZ were lower in plasma collected in Vacutainers than in plasma from Venoject tubes (Table 1). The mean concentration in plasma from Vacutainer

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Table 1
Chlorpromazine concentrations (ng ml^{-1}) in plasma collected simultaneously with Vacutainer and Venoject tubes

Patient	Venoject	Vacutainer	% Difference
1	808	713	−12
2	136	116	−15
3	136	76	−28
4	119	104	−13
5	114	102	−11
6	97	92	−5
7	61	71	6
8	51	39	−24
9	51	36	−29
10	28	23	−18
11	28	19	−32
12	20	15	−25
13	15	15	0
14	15	9	−40
15	14	13	−7
16	8	14	75
17	7	10	43
18	7	7	0
19	5	5	0
20	1	1	0
21	0	0	0

tubes was 71 ± 152 ng ml^{-1} (standard deviation) whereas that in plasma from Venoject tubes was 81 ± 172 ng ml^{-1}. This difference was statistically significant ($t = 2.17$; 20 degrees of freedom; $p < 0.05$, two-tailed). The reduction in concentration was noted in samples from seven of the eight patients with concentrations within the estimated range of optimal therapeutic efficacy, 40–300 ng ml^{-1} [14, 15, 18], and in samples from the one patient with a supra-optimal concentration. The reduction was also noted in samples from five of the twelve patients with concentrations below the optimal range although no difference was detectable in samples from the six patients with concentrations less than 10 ng ml^{-1}.

It has been reported that reduction in plasma concentrations of various drugs may occur when blood samples are collected in Vacutainer tubes; this effect has been described with quinidine [4–6], lidocaine (lignocaine) [7], propranolol [1], alprenolol [2] and meperidine (pethidine) [3]. Similar effects have been reported with tricyclic antidepressants [8–10] and have also been noted for CPZ by Midha *et al.* [19] who used a radioimmunoassay. The same effect also occurs with the neuroleptics trifluoperazine and fluophenazine [20].

The reduction is apparently dependent on contact with the stopper which contains a plasticizer, tri(2-butoxyethyl)-phosphate; this plasticizer causes displacement of the drug from protein binding with resultant uptake of the free drug by erythrocytes. The effect can be avoided by rigorously keeping the collection tubes upright, which is usually not practical, or by the use of other containers such as Venoject tubes.

Patients receiving the same dose of CPZ can differ markedly in their steady-state plasma concentrations of CPZ [13, 15, 16], and plasma concentrations of CPZ may be better correlated with therapeutic effects [14, 15, 18] or toxic effects [12, 14, 15, 21] than

are doses. Thus measurement of plasma concentrations of CPZ may have a role in the clinical management of patients.

The method of sample collection needs to be taken into account by clinicians and investigators when plasma concentrations of CPZ and other neuroleptics are considered. It is a possible source of within-centre variation as well as of differences between centres.

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