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Potential for drug interactions involving cytochrome P450 in patients attending palliative day care centres: a multicentre audit

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Aim
To determine the potential for drug interactions involving cytochrome P450 (CYP) in patients receiving palliative day care.

Methods
Drugs used by patients attending four specialist palliative day care centres were reviewed to identify combinations that could result in a pharmacokinetic interaction via any of the five main human forms of CYP.

Results
Of 160 patients, 145 (91%) were prescribed at least one drug that was a substrate, inhibitor or inducer of one of the five main CYP isoforms. Twenty-four drug combinations, involving 34 patients, could have given rise to a clinically important interaction.

Conclusions
Prescribers should be aware that in this group of patients, one in five are at risk of a clinically important CYP-mediated drug interaction.

Introduction

Each week in the UK, several thousand patients attend specialist palliative care day centres [1]. Most of these patients are likely to be elderly with advanced cancer and to be taking multiple drugs both regularly and *pro re nata* (p.r.n.) to relieve symptoms related to cancer and for other chronic conditions. Apart from at the day centre, these patients may also receive drug prescriptions from hospital clinics or general practitioners. As the number of different drugs increases, so does the risk of

a drug–drug interaction, especially if an accurate drug history or knowledge of the potential consequences is lacking.

One important cause of drug interactions is the inhibition or induction of the activity of the cytochrome P450 (CYP) group of enzymes that are involved in the metabolism of many drugs [2, 3]. The aim of this audit was to identify and quantify the drug combinations that could result in clinically important interactions mediated by CYP in patients attending palliative care day centres, in order to raise awareness and aid safer prescribing.

Methods

Patients attending four adult specialist palliative care day centres during 1 week in September 2003 were audited. At all the day centres, patients have a medication card that is updated every time the drug regimen is altered. The copy kept in the nursing notes was used to record drugs taken orally or parenterally on a regular and p.r.n. basis onto an anonymized proforma so that individual patients were not identifiable. Permission to audit the prescription data was granted by the medical directors of each unit.

Five isoforms of CYP are mainly responsible for drug metabolism, i.e. CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A [2] and only drug–drug interactions involving these were considered. For each patient, the likelihood of a CYP-mediated interaction between individual drug combinations was assessed based on a search of established databases (Web of Science, PubMed, http://www.gentest.com/human_p450_database/index.html), Stockley's 'Drug Interactions' [2] and personal files of one of the authors (M.S.L.). They were categorized as either (i) *clinically important interaction*, for which there is *in vitro* metabolic evidence and/or *in vivo* pharmacokinetic and clinical evidence that a drug–drug interaction occurs or could occur; (ii) *potentially clinically important interaction*, for which there is a theoretical basis for an interaction, but for which experimental evidence is lacking; or (iii) *unlikely interaction* for which there is either evidence against or no theoretical basis for an interaction [4].

Results

The prescription charts of 160 patients, 87 (54%) males with a median (range) age of 71 (25–97) were audited. All except eight (5%) had cancer (motor neurone disease five, multiple sclerosis three). Patients took a median (range) of six (0–16) and one (0–6) regular and p.r.n. drugs, respectively, a combined total of seven (1–17) different drugs. The majority of patients (145, 91%) received one (22, 14%) or two or more drugs (123, 77%) that were substrates, inhibitors or inducers of one of the five CYP isoforms with a median (range) of four (0–12) drugs. Two hundred and thirty-three, 146, 137, 63 and 12 prescriptions were written for drugs interacting with CYP3A, CYP2C19, CYP2D6, CYP2C9 and CYP1A2, respectively. Twenty-four drug combinations were categorized as giving rise to clinically important or potentially clinically important interactions, affecting 34 patients (Table 1). A further 30 combinations were considered unlikely to cause an interaction and are not detailed further.

Discussion

The results of this audit represent a 'snapshot' of the number of drugs received by patients attending four specialist palliative care centres. With a median of seven different drugs, our results confirm that polypharmacy is common in patients receiving palliative care [5, 6]. This polypharmacy resulted in the patients receiving a median of four drugs that were either substrates, inhibitors or inducers of one of the five main CYP isoforms, and one in five patients were receiving combinations of drugs that give rise to clinically important or potentially clinically important drug–drug interactions involving CYP. The impact of a drug–drug interaction can be influenced by a number of factors, e.g. age, physical health and genetic polymorphism in some of the main CYP isoforms, most notably CYP2D6, which affects enzyme function. As many patients receiving palliative care are elderly and frail this population may be particularly susceptible to the effects of a drug–drug interaction.

The two clinically important interactions were between omperazole and diazepam that results in increased diazepam concentrations and between phenytoin and dexamethasone that results in reduced dexamethasone concentrations [7, 8]. Failure to recognize the former could result in an increase in drowsiness being falsely attributed to disease progression, whereas failure to consider the latter could result in a patient receiving a suboptimal dose of dexamethasone.

Altogether, of the 24 clinically important or potentially clinically important drug–drug interactions involving CYP, half were associated with corticosteroids (dexamethasone or prednisolone) [9, 10], and a quarter with analgesics, notably codeine and oxycodone [11, 12]. Given the high frequency of use in this group of

Table 1
Drug combinations taken by patients attending palliative care day centres that give rise to (i) clinically important and (ii) potentially clinically important drug–drug interactions involving cytochrome P450

Category*	Drug combination	Frequency	Drug effect increased (↑) or decreased (↓)
(i) 'important'	Omeprazole + diazepam	3	Diazepam↑
	Phenytoin + dexamethasone	2	Dexamethasone↓
(ii) 'potentially important'	Dexamethasone + temazepam	5	Temazepam↓
	Haloperidol + oxycodone	4	Oxycodone↓
	Levomepromazine + oxycodone	3	Oxycodone↓
	Prednisolone + diazepam	3	Diazepam↓
	Dextropropoxyphene + tramadol	2	Tramadol↑
	Carbamazepine + zopiclone	1	Zopiclone↓
	Coproxamol + codeine	1	Codeine↓
	Dexamethasone + amitriptyline	1	Amitriptyline↓
	Dexamethasone + fentanyl	1	Fentanyl↓
	Dexamthasone + quinine	1	Quinine↓
	Dexamethasone + simvastatin	1	Simvastatin↓
	Dexamethasone + tacrolimus	1	Tacrolimus↓
	Dexamethasone + zopiclone	1	Zopiclone↓
	Fluoxetine + codeine	1	Codeine↓
	Haloperidol + codeine	1	Codeine↓
	Levomepromazine + haloperidol	1	Levomepromazine↑ haloperidol↑
	Levomepromazine + tamoxifen	1	Tamoxifen↓
	Prednisolone + amlodipine	1	Amlodipine↓
	Prednisolone + fentanyl	1	Fentanyl↓
	Prednisolone + trazodone	1	Trazodone↓
	Prednisolone + zopiclone	1	Zopiclone↓
	Verapamil + zopiclone	1	Zopiclone↑
	Total	39	
	No. (%) of patients with at least one (i) or (ii) interaction	34 (21%)	

**For definitions, see Methods.*

patients, possible interactions involving these drugs could be the focus for future *in vivo* research. Future work could also consider pharmacodynamic interactions or the potential for drug interactions with complementary/alternate medicines (e.g. St John's Wort) that are increasingly popular in this group of patients.

In conclusion, this audit highlights the need for palliative care, community and hospital practitioners who prescribe or give prescribing advice to be alert to the risks that polypharmacy brings to this group of patients, and to consider routinely the possibility of an important drug–drug interaction when prescribing additional drugs.

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