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Exercises in Clinical accuracy checking

By BRIDGET FEATHERSTONE, DIPCLINPHARM, MRPHARMS, and ALISON EGGLETON, MSc, MRPHARMS

These checking exercises attempt to address the pharmaceutical and medical issues that arise in different specialties. This month, the subject is organ transplantation. Although few hospitals undertake transplant surgery, transplant patients will take immunosuppressive therapy for life. Pharmacists may be involved in caring for this patient group when they are admitted to hospital for reasons other than transplantation.

Mrs Featherstone is lead pharmacist for transplantation and surgery, and Mrs Eggleton is principal pharmacist, education and training, at Addenbrooke's Hospital, Cambridge

Readers are invited to identify the problems and determine solutions for them. The prescriptions are followed by a discussion of the significant issues.

It must be emphasised that these tests were introduced to assess the performance of checkers in a dispensary situation where time is at a premium. It should also be noted that these prescriptions have passed through the dispensary at Addenbrooke's NHS Trust, although the patients' names have been removed to maintain confidentiality. The check list used by candidates is shown in Figure 1. Figures 2, 3, 4 (p73) and 5 (p74) relate to prescription 1, and Figures 6 (p77) and 7 (p78) relate to prescription 2.

CLINICAL ACCURACY CHECKING TEST

<p>Task</p> <p>1. You have minutes to review the following prescription charts and identify the problems. You have minutes to document your answers Total time allowed: minutes</p> <p>2. You are only able to make ONE intervention per prescription For each of the prescriptions, using the answer sheets provided:</p> <p>3. Document the ward and clinical specialty</p> <p>4. List briefly the endorsements you would make to the chart</p> <p>5. List briefly the patient's major medical problem(s) suggested by the drug therapy</p> <p>6. List briefly the most important pharmaceutical problems you would try to resolve if you were checking the chart on a ward (maximum of SIX problems)</p> <p>7. State the ONE priority intervention you would make for EACH of the charts given that you are checking the chart in the dispensary (NB: Occasionally, more than one intervention may be needed)</p> <p>8. Briefly state the action you would take to resolve the priority intervention</p> <p>9. State the urgency of the priority intervention from one of the following: Urgent = chart must be amended by a doctor or pharmacist before being dispensed Less urgent = any other action, such as sending an intervention note to the doctor, highlighting the problem to the ward pharmacist, telephoning a nurse or doctor for further information</p> <p>10. Materials allowed:</p> <table border="0"> <tr> <td>Martindale's Extra Pharmacopoeia</td> <td>BNF</td> </tr> <tr> <td>Paediatric formulary</td> <td>Hospital formulary</td> </tr> <tr> <td>Compendium of data sheets and SPCs</td> <td>Calculator</td> </tr> <tr> <td>Trissel's handbook of injectable drugs</td> <td>Hospital IV monographs</td> </tr> <tr> <td>Renal drug handbook</td> <td></td> </tr> <tr> <td>List of wards — specialty and current ward pharmacist</td> <td></td> </tr> </table>	Martindale's Extra Pharmacopoeia	BNF	Paediatric formulary	Hospital formulary	Compendium of data sheets and SPCs	Calculator	Trissel's handbook of injectable drugs	Hospital IV monographs	Renal drug handbook		List of wards — specialty and current ward pharmacist		<p>Answer sheet (Candidate name:.....)</p> <p>Prescription number 1</p> <p>Review panel:</p> <p>Ward Clinical specialty</p> <p>Chart endorsements:</p> <p>Medical problems:</p> <table border="0"> <tr> <td>1.</td> <td>5.</td> </tr> <tr> <td>2.</td> <td>6.</td> </tr> <tr> <td>3.</td> <td>7.</td> </tr> <tr> <td>4.</td> <td>8.</td> </tr> </table> <p>Pharmaceutical problems:</p> <table border="0"> <tr> <td>1.</td> <td>4.</td> </tr> <tr> <td>2.</td> <td>5.</td> </tr> <tr> <td>3.</td> <td>6.</td> </tr> </table> <p>Priority intervention number 1 2 3 4 5 6 (circle the appropriate number)</p> <p>Suggested action to resolve the priority intervention:</p> <table border="0"> <tr> <td>Urgency:</td> <td>Urgent</td> <td>Less urgent</td> </tr> <tr> <td>(circle as appropriate)</td> <td></td> <td></td> </tr> </table>	1.	5.	2.	6.	3.	7.	4.	8.	1.	4.	2.	5.	3.	6.	Urgency:	Urgent	Less urgent	(circle as appropriate)		
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Figure 1: Instructions for candidates: state the ward and clinical specialty in order to focus attention on likely problems. For example, if the patient was on a medical ward specialising in renal disease, the pharmacist must be particularly vigilant about renally excreted drugs. The chart endorsements refer to the discharge or to take out (TTO) prescription where one exists or otherwise to the inpatient chart. Please note: candidates are given six minutes to review each prescription, and three minutes to document their answers for each prescription

DRUG (APPROVED NAME)				Date	6	6	6	7	7
Morphine									
Dose	Max Frequency	Route	Start Date	Time	13.00	17.00	21.00	5.00	10.00
1.0mg	4 hourly	IV	06.06.02						
Signature A Doctor		Stop Date	Pharm	Dose	10mg IV	10mg IV	10mg IV	10mg IV	10mg IV
Additional Instructions / Max. dose in 24 hours				Given by	AN	AN	AN	AN	AN
DRUG (APPROVED NAME)				Date	6	6			
Cyclizine									
Dose	Max Frequency	Route	Start Date	Time	13.00	21.00			
5.0mg	TDS	IV	06.06.02						
Signature A Doctor		Stop Date	Pharm	Dose	50mg IV	50mg IV			
Additional Instructions / Max. dose in 24 hours				Given by	AN	AN			

Figure 5: Patient's "as required" drugs (prescription 1)

The patient can be identified easily as a renal transplant patient because the prescription includes typical "renal" drugs such as calcium carbonate and epoetin. Basiliximab is also used in the immunosuppressive regimen for renal rather than liver transplant.

Immunosuppression is vital in order to minimise the risk of organ rejection. The Addenbrooke's renal transplant protocol uses a quadruple immunosuppressive regimen. The theoretical basis of quadruple therapy is to allow lower doses of individual agents to be used. This helps to minimise the risk of side effects to the patient without compromising immunosuppression. All patients receive basiliximab and prednisolone. They will also receive either ciclosporin or tacrolimus, and either azathioprine or mycophenolate mofetil, depending upon their risk of rejection. The regimen selected here (ciclosporin, azathioprine, prednisolone and basiliximab) is appropriate for a renal transplant patient considered at low risk of rejection.¹ The National Institute for Clinical Excellence (NICE) is in the process of developing guidelines in this clinical area. When ciclosporin is prescribed, the brand name (Neoral) should be used to avoid confusion with Sandimmun which has different bioavailability.

Following transplantation, all patients are at risk of infection. This is because immunosuppressive therapy suppresses cell-mediated immunity, thus increasing the risk of opportunistic infection with viral, fungal and parasitic organisms. Flucloxacillin is given prophylactically at the time of transplantation to reduce the risk of staphylococcal infection because of commensal bacteria on the skin. Following the transplant, patients at Addenbrooke's Hospital receive prophylactic therapy routinely with co-trimoxazole and amphotericin lozenges or nystatin suspension. Ganciclovir is given if there is a cytomegalovirus (CMV) mismatch. This means that the organ transplanted was positive for CMV but the organ recipient was negative for CMV. The patient also receives isoniazid if there is a risk of tuberculosis (TB). The ward pharmacist, not the dispensary pharmacist, should have the responsibility of checking the patient's TB and CMV risk status.

Co-trimoxazole is included in the protocol to reduce the risk of *Pneumocystis carinii* pneumonia (PCP). If tolerated, co-trimoxazole at various doses has been shown to be more effective than other drugs at reducing the incidence of PCP.² The co-trimoxazole dose on this prescription may be considered low, even for a prophylactic dose. This dose has been included in the Addenbrooke's post-renal transplant protocol for a number of years and, to date, PCP has not been a problem, although possibly, evidence to support this dose is lacking. The dispensary pharmacist must be aware of different doses of co-trimoxazole in different immunosuppressive regimens, for example, following cancer chemotherapy or radiotherapy and in patients infected with human immunodeficiency virus (HIV). In HIV patients, for example, a dose of 960mg three times a week is commonly used, with a failure rate of 1.8 per cent over one year.²

Following transplantation, patients are at risk of thrombosis which can have devastating consequences, including graft loss. It is routine practice at Addenbrooke's to give low dose enoxaparin in the immediate post-operative period and convert this to low dose aspirin at

around the time of discharge. Although this is established practice in a number of centres, there are few published data regarding the use of low molecular weight heparins in thromboprophylaxis post-renal transplant. The former practice of giving both aspirin and enoxaparin in the immediate post-transplant period was stopped due to a number of cases of bleeding complications.

The dispensary pharmacist should be aware that some medicines given pre-transplant, when the patient would have been on dialysis, must be reviewed. This prescription still includes a number of pre-transplant drugs such as epoetin, ferrous sulphate and calcium carbonate chewable tablets which will no longer be required and should be stopped. As renal function improves over time following transplantation, the doses of remaining drugs must be reviewed. This period will vary considerably between patients. Blood pressure will be closely monitored in hospital and post-discharge, and the doxazosin dose may be adjusted to keep blood pressure within accepted limits defined by the British Hypertension Society (systolic less than 140mmHg, diastolic less than 85mmHg).³

Allopurinol and atorvastatin are likely to be required post-transplant. Hyperuricaemia is common in renal transplant patients treated with ciclosporin. The current allopurinol dose has been adjusted for dialysis to be the same as for severe renal impairment as suggested in the 'Renal drug handbook'.⁴ The dose should be changed in line with improving renal function. The lipid profile may change post-transplant and is often found to deteriorate. Therefore, the atorvastatin dose may also need to be increased to keep the patient's serum cholesterol within reference range adjusted according to the patient's cardiovascular risk factors (often quoted as less than 5mmol/L). The time to peak effect of statins tends to be about four to six weeks⁵ so again, the patient's cholesterol level and statin dose will require monitoring both in hospital and post-discharge.

The main area of concern on this prescription is the well-recognised drug interaction between azathioprine and allopurinol.⁶ Azathioprine is metabolised in the liver to mercaptopurine, which is then oxidised by xanthine oxidase to an inactive compound, 6-

thiouric acid. Allopurinol inhibits the xanthine oxidase resulting in an accumulation of mercaptopurine and a significant increase in toxic effects, notably thrombocytopenia, leucopenia and anaemia. If allopurinol is to be continued, it is imperative that the azathioprine dose is reduced to a third or a quarter of the standard dose. An alternative would be to replace azathioprine with mycophenolate mofetil because this drug is not affected by the interaction.⁷

There is also a potential drug interaction between atorvastatin and ciclosporin.⁸ The risk is two-fold. Firstly, muscle-related side effects such as myopathy and rhabdomyolysis have been reported with both drugs.^{9,10} Secondly, Stockley reports one case where ciclosporin levels were increased by between 26 per cent and 54 per cent in post-renal transplant patients treated with atorvastatin 10mg daily.¹¹ Those

Prescription Chart											
Patient Details				DRUG SENSITIVITIES							
Surname		Hospital No		Weight		Doctor must also enter this information on FRONT of case folder must not be administered unless this box has been completed					
First Names		Date of Birth	Sex	64.5kg		Date	Drug/Substance		Signature		
V		04.05.53	F	Height		03.05.02	NKDA		A DOCTOR		
Consultant		Ward									
		Transplant									
Regular Prescriptions					Regular Prescriptions						
Month and date					Month and date						
Tick times or enter other times					Tick times or enter other times						
DRUG (APPROVED NAME)					DRUG (APPROVED NAME)						
Tacrolimus					Fluconazole						
Dose	Route	Start Date	Stop Date	6	8	*	AN	6	8	*	AN
3mg	PO/IV	03.05.02		12	14			12	14		
Signature		A Doctor		Pharm				Signature		A Doctor	
Additional Instructions								Additional Instructions			
DRUG (APPROVED NAME)					DRUG (APPROVED NAME)						
Azathioprine					Ranitidine						
Dose	Route	Start Date	Stop Date	6	8	*	AN	6	8	*	AN
50mg	PO/IV	03.05.02		12	14			12	14	*	
Signature		A Doctor		Pharm				Signature		A Doctor	
Additional Instructions								Additional Instructions			
DRUG (APPROVED NAME)					DRUG (APPROVED NAME)						
Methylprednisolone					Enoxaparin						
Dose	Route	Start Date	Stop Date	6	8	*	AN	6	8	*	AN
20mg	PO/IV	03.05.02		12	14			12	14		
Signature		A Doctor		Pharm				Signature		A Doctor	
Additional Instructions								Additional Instructions			
DRUG (APPROVED NAME)					DRUG (APPROVED NAME)						
Ganciclovir											
Dose	Route	Start Date	Stop Date	6	8	*	AN				
1g	PO/IV	03.05.02		12	14	*					
Signature		A Doctor		Pharm				Signature			
Additional Instructions								Additional Instructions			

Figure 6: Patient's details and regular drugs (prescription 2)

DRUG (APPROVED NAME)				Date	4	5	6	7	8
Morphine									
Dose 10mg	Max Frequency 4 hourly	Route IV	Start Date 03.05.02	Time 10.00					
Signature A Doctor		Stop Date	Pharm	Dose 10mg					
Additional Instructions / Max. dose in 24 hours				Route IV					
				Given by A N					
DRUG (APPROVED NAME)				Date					
Metoclopramide									
Dose 10mg	Max Frequency TDS	Route PO/IV	Start Date 03.05.02	Time					
Signature A Doctor		Stop Date	Pharm	Dose					
Additional Instructions / Max. dose in 24 hours				Route					
				Given by					

Figure 7: Patient's "as required" drugs (prescription 2)

water-soluble statins which are not metabolised via the cytochrome P450 system, such as pravastatin, may provide a safer alternative although efficacy may be compromised.¹² Stockley reports several studies where the concurrent use of pravastatin and ciclosporin showed no increase in side effects and no change in ciclosporin levels. However, there is one report of pravastatin serum levels being increased by ciclosporin in a group of transplant patients. In practice, atorvastatin is prescribed with ciclosporin and, as with all statins, the patients are counselled to report any signs of muscle pain or weakness. It should be noted that atorvastatin can increase the ciclosporin serum level and so care will be needed during the titration period to establish the optimum dose of both drugs.¹¹

A competent pharmacist should be aware of the need to review drug therapy post-operatively and in accordance with changing renal function, and be able to recognise and advise on the significance of the drug interactions.

PRESCRIPTION 2

Figure 9 (p80) shows the solution to prescription 2. This prescription is for a 49-year-old female, Mrs B, who has recently undergone an orthotopic liver transplant (OLT). Orthotopic simply means that the new liver is put in place of the old liver. The main medical problems are risk of rejection and risk of infection, as for prescription 1. Because of the impairment of blood clotting associated with liver disease, in this patient the risk of thrombosis post-surgery must be weighed against the risk of bleeding. This patient also has problems tolerating oral medication and conversion to the intravenous drug route is an important pharmaceutical care issue.

It is more difficult to identify a liver transplant patient simply by looking at the medication because the obvious signs found on the chart of a renal patient, such as the use of epoetin, are absent. At Addenbrooke's, all first-time recipients of a liver transplant receive triple immunosuppressive therapy with tacrolimus, azathioprine and prednisolone. Again, triple therapy is used to allow lower doses of individual drugs to be used, thus minimising toxicity without compromising immunosuppression. Tacrolimus is now used as a first-line immunosuppressive agent in place of ciclosporin following results of the TMC trial.¹³ This trial showed a better clinical outcome at one year in patients treated with tacrolimus than in those treated with microemulsified ciclosporin (Neoral). Using tacrolimus post-liver transplant has also been shown to have economic benefits.¹⁴

Post-liver transplant patients have an increased risk of infection, including opportunistic infections. Fungal infections are a particular risk post-OLT because they lead to greater morbidity and prolonged hospital stay. Hence, it is routine for all liver transplant patients at Addenbrooke's Hospital to receive prophylactic fluconazole which is continued until around the time of discharge when it is converted to oral nystatin. The interaction between fluconazole and tacrolimus is well recognised.¹⁵ Although the mechanism is not fully established,

the evidence suggests that fluconazole inhibits cytochrome P450 CYP3A4 enzymes thus reducing the metabolism of tacrolimus and increasing blood levels. A fluconazole dose of 100mg daily will potentially increase tacrolimus levels in the order of 1.4-fold. The tacrolimus blood level is monitored routinely post-OLT and it is usual for tacrolimus and fluconazole to be prescribed together as part of the infection prophylaxis protocol. Therefore, it should not be necessary for the dispensary pharmacist to intervene on this potential drug interaction in the immediate post-transplant period. In patients not in the immediate post-transplant period who have been stabilised on tacrolimus and who have been started on fluconazole, it would be prudent for the pharmacist to confirm that the prescriber is aware of this interaction.

Cytomegalovirus (CMV) infection also poses a severe risk post-transplantation, especially in the group of patients who are seronegative for CMV and who receive a donor liver that is seropositive for CMV. Oral ganciclovir (1g three times a day) has been shown to be a safe and effective method for the prevention of CMV in this patient group and is used routinely at Addenbrooke's.¹⁶

The main pharmaceutical care issue on this prescription is the conversion of oral to intravenous therapy. The doses of fluconazole and prednisolone are the same whether given orally or intravenously. However, the conversion of both tacrolimus and ganciclovir is inappropriate. It is exceptionally rare to see intravenous tacrolimus prescribed, because even immediately post-OLT, it can usually be given enterally, either swallowed or via a nasogastric tube. It would be worth contacting the ward staff to ascertain the reason for intravenous use and whether there is any possibility that it could be given enterally. If the intravenous route is considered essential, the recommended intravenous tacrolimus dose immediately post-OLT is 0.01 to 0.05mg/kg over 24 hours. This is 50 per cent or less of the recommended oral dose of 0.05mg/kg twice daily.¹⁷ Hence, this prescription has the potential to overdose the patient and must be amended before intravenous tacrolimus is dispensed. It is worth mentioning that once patients have been stabilised on an oral tacrolimus dose, one-fifth of the oral dose can be given intravenously. This was the recommendation given to Addenbrooke's by the manufacturers.

The ganciclovir dose of 1g three times a day is correct if the drug is given orally, assuming the patient has normal renal function. However, the recommended intravenous dose is 5mg/kg (approximately 325mg in this patient) twice a day.¹⁸ This prescription would result in an overdose for the patient and it must be amended urgently.

A competent pharmacist should be expected to check that the dose of all drugs has been converted correctly when medication is changed from oral to intravenous administration. The pharmacist should also be aware of the risk of a drug interaction between fluconazole and tacrolimus.

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Exercises in clinical accuracy checking

Exercises in clinical accuracy checking have been appearing in *Hospital Pharmacist* since June 2000. The idea for the series came from Alison Eggleton, principal pharmacist, education and training at Addenbrooke's Hospital, Cambridge. Since then, all the exercises have been taken from actual prescriptions presented to the dispensary at Addenbrooke's Hospital.

Hospital Pharmacist would like to extend the series by asking pharmacists at other hospitals to submit pharmaceutical problems seen in their hospitals.

General advice for contributors can be found at www.pjonline.com but it has to be stressed that authors must also be aware that the problems are to assess the performance of checkers in a dispensary situation where time is at a premium. It should not take candidates more than six minutes to review each prescription, and three minutes to document their answers for each prescription.

Advertisement

Prescription number 1

Ward: Surgical Clinical specialty: Transplant

Chart endorsements:

1. Ciclosporin = Neoral
2. Simulect = basiliximab
3. Septrin = co-trimoxazole
4. Calcichew = calcium carbonate chewable 500mg, take with meals
5. Neorecormon = epoetin beta

Medical problems:

1. Post-renal transplant: risk of rejection, risk of infection, risk of thrombosis
2. Hyperuricaemia
3. Hypercholesterolaemia
4. Hypertension
5. Pain control

Pharmaceutical problems:

1. Interaction: allopurinol and azathioprine
2. Interaction: atorvastatin and ciclosporin
3. Review of medication taken pre-transplant
4. Review of allopurinol dose
5. Review of atorvastatin dose

Priority intervention Number 1 but must also mention number 3

Suggested action to resolve the priority intervention:

Contact the prescriber to discuss the continued need for pre-transplant medication (calcium carbonate, epoetin, ferrous sulphate). Inform the prescriber of the need to reduce azathioprine dose should allopurinol continue

Urgency: Urgent

Figure 8: Solution to prescription 1

Prescription number 2

Ward: Surgical Clinical specialty: Transplant

Chart endorsements:

Tacrolimus IV — administer through a non-PVC giving set over 24 hours

Medical problems:

1. Post-liver transplant: risk of rejection, risk of infection, risk of thrombosis
2. Pain control
3. Inability to tolerate oral drugs

Pharmaceutical problems:

1. Interaction: tacrolimus and fluconazole
2. Inappropriate dose conversion from IV to oral route: ganciclovir and tacrolimus

Priority intervention Number 2

Suggested action to resolve the priority intervention:

Contact the prescriber to find out if tacrolimus must be given intravenously or if enteral route is possible. Advise on correct dosage schedule for IV or oral/nasogastric route as appropriate. Advise on correct dosing schedule for IV ganciclovir

Urgency: Urgent

Figure 9: Solution to prescription 2