Development, implementation and cost-effectiveness of a protocol for review of combination diuretic prescribing

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Aims To determine the extent of inappropriate prescribing of combination diuretics and the cost implications of protocol implementation.

Methods Pharmacist-run medication review clinics in two general practices in Bradford, UK.

Results Sixty-one patients, mean $\pm$ s.d. age 75.8 ± 12.0 years, were reviewed. Thirty-six met protocol criteria; 30 (49.2%) patients had their potassium-sparing diuretics (PSDs) discontinued. Mean (95% confidence interval) reduction in serum potassium concentrations after intervention in these 30 patients was 0.26 (0.09 , 0.43) mmol l^{-1} ($P < 0.01$). Twenty-eight (93.3%) patients were within the reference range at follow-up; none was below.

Conclusions Of prescribed PSDs, 59% were found to be unnecessary. Using the developed protocol potentially improves drug safety and enables cost savings.

Keywords: combination diuretic, cost-effectiveness, hyperkalaemia, hypokalaemia, medication review, pharmacist intervention, potassium-sparing diuretic

Introduction

Hypokalaemia can occur after initiation of thiazide or loop diuretics [1, 2] and this can usually be rectified by the addition of a potassium-sparing diuretic (PSD) [3]. There is anecdotal evidence that PSDs are prescribed prophylactically, under the inappropriate assumption [4] that they negate the need for follow-up electrolyte monitoring. Routine prescribing of PSDs is unwarranted except in patients at risk from hypokalaemia [5] and in those who develop hypokalaemia with diuretics [1, 6, 7].

The elderly, patients with renal impairment, and those prescribed concomitant angiotensin-converting enzyme inhibitors (ACE inhibitors) are particularly susceptible to developing hyperkalaemia with PSDs [5–8]. PSDs should be avoided or used with caution in such patients [9] as hyperkalaemia is more likely to cause life-threatening arrhythmias and sudden death than hypokalaemia [4, 8].

Although combination diuretics, containing either a loop or thiazide diuretic together with a potassium-sparing diuretic, have been developed to aid compliance, they are not generally recommended [1, 9]. Combination

diuretics do not allow easy dosage adjustment and are generally more expensive than prescribing the two components separately [1]. Consequently combination products were one of the areas targeted by the Audit Commission's 1994 report [10].

The aims of this study were to develop and implement a protocol for the review of patients prescribed PSDs in primary care and to determine the cost of its implementation.

Methods

Participants

Two medical practices with a combined total patient population of 13 900 were arbitrarily chosen from the five fund-holding medical practices in which the pharmacist, with 3 years' postgraduate community experience, was employed. Seven FTE general practitioners (GPs) were employed in total in the two practices and both were GP training practices. No interventions on diuretic prescribing had been implemented prior to the intervention, and no electronic reminders were available regarding PSDs on either practice's electronic prescribing system.

Patients identified by electronic search of practice records as receiving combination diuretics were invited by letter to attend a pharmacist-run medication review

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clinic. Nonresponders were followed up by telephone. Nonattendees were offered a second appointment.

Sample size calculation

Based on the assumption that the population mean $\pm$ s.d. potassium serum concentration is 4.3 ± 0.4 and that a 0.3 ± 0.5 difference would need to be detected with 90% power, a sample size of 24 was calculated as being required (using a normal approximation and assuming that the change would be in one direction).

PSD review protocol

There were no local guidelines available regarding the prescribing of PSDs. The following protocol for PSD review was agreed upon after discussion with the GPs working within the two medical practices.

1. Baseline electrolytes and renal function checked.
2. PSDs are considered to be inappropriate, and discontinuation recommended when:
 - creatinine clearance (CrCl) $< 20 \text{ ml min}^{-1}$ (moderate to severe renal impairment) [7, 9]
 - serum K $\geq 4.0 \text{ mmol l}^{-1}$ for patients not at risk of cardiac arrhythmias [2]
 - Serum K $\geq 4.5 \text{ mmol l}^{-1}$ for patients prescribed concurrent digoxin or antiarrhythmic drugs [7].
3. Serum electrolytes re-checked 2–8 weeks after PSD discontinuation [2].

Process of review

For all ambulatory patients reviews were undertaken within the medical practice. Patients unable to attend physically were visited at home.

Patients received counselling on their drug therapy and diuretics were reviewed according to protocol. The pharmacist, a trained phlebotomist, took all appropriate samples. Renal function was estimated using the Cockcroft and Gault method [11]. Proposed medication changes were documented in each patient's computerized records and discussed with their GP. Agreed medication changes were communicated to the patient and drug-monitoring plans were placed in the medical records.

Outcome measurements

Information relating to age, sex, current drug therapy and most recent biochemical test results, serum concentrations and prescribed medication before and after intervention was collected for each patient.

Medical records were reviewed after 6–12 months to determine whether the drug changes implemented had been maintained.

Cost analysis

A cost analysis of the pharmacist service was performed with average time spent as a result of the review by the pharmacist and GPs determined from actual values from a small sample of reviews.

The cost per potential case of hyperkalaemia prevented was estimated, based on cost of service provision and excluding drug cost savings. A sensitivity analysis was performed based on the extreme incidences of hyperkalaemia expected, 1–10% for all patients [6–9], and the actual incidence recorded.

Drugs

Some of the combination preparations were prescribed generically, others by brandname. Brands used were:

- Amiloride & frusemide (total 48 patients): Frumil[®], Helios; Fru-Co[®], Ivax; Lasoride[®], Borg.
- Triamterine & frusemide (total 4 patients): Frusene[®], Orion.
- Amiloride & bumetanide (1 patient): Burinex-A[®], Leo.
- Amiloride & hydrochlorothiazide (total 5 patients): Moduretic[®], Du Pont; Amil-Co[®], Ivax.
- Triamterine & hydrochlorothiazide (total 2 patients): Dyazide[®], Goldshield; Triam-Co[®], Ivax.
- Amiloride & cyclopenthiazide (1 patient): Navispare[®], Navartis.

Results

One hundred and ten patients were identified for inclusion (0.79% of the practice population). Sixty-one patients were reviewed. Reasons for dropout were refusal or repeated nonattendance at the clinic ($n = 20$) discontinuation of PSD before the study ($n = 10$), complete discontinuation of diuretic therapy ($n = 4$), death ($n = 12$), and leaving the practice ($n = 3$).

Fifty-one (83.6%) of the reviewed patients were female, their mean $\pm$ s.d. age was 75.8 ± 12.0 years (range 39–99) and the mean $\pm$ s.d. number of drugs on repeat prescription was 5.2 ± 2.4 (range 1–11). No significant differences in recorded demographic characteristics were found between identified patients who had and had not been reviewed.

Fifty-three (86.9%) of patients were prescribed a loop diuretic (52 frusemide, 1 bumetanide) and the remaining eight (13.1%) patients were prescribed a thiazide. Fifty-five patients were prescribed amiloride (87.3%) and the remaining six (12.7%) were prescribed triamterene concurrently with their loop or thiazide diuretic. No patients were concomitantly prescribed ACE inhibitors.

The mean $\pm$ s.d. baseline serum potassium and sodium concentrations were 4.19 ± 0.51 mmol l^{-1} and 139.7 ± 2.4 mmol l^{-1} , respectively. Thirteen (21.3%) patients had no renal impairment, 39 (63.9%) had mild impairment and nine (14.8%) had moderate impairment. Of the three patients with serum potassium concentration >5 mmol l^{-1} at baseline, two had mild renal impairment and one had normal renal function.

Thirty-six patients (59.0% of those reviewed) met the criteria for PSD discontinuation: nine patients had $\text{CrCl} < 20$ ml min^{-1} , 25 patients not at risk of cardiac arrhythmias had serum K ≥ 4.0 mmol l^{-1} , and two patients prescribed concurrent digoxin or antiarrhythmic drugs had serum K ≥ 4.5 mmol l^{-1} . PSDs were discontinued in 30 patients (49.2% of those reviewed); two patients refused the change, two died before the change was carried out (deaths unrelated to study), and in two patients the change had not been implemented 6 months following review.

Figure 1 gives the serum potassium concentrations at baseline and 2–8 weeks after PSD discontinuation. No patient had a serum potassium concentration below the reference range (3.5–5.0 mmol l^{-1}), and there were no adverse clinical sequelae recorded following PSD discontinuation. The mean reduction in serum potassium concentration after PSD discontinuation was 0.26 mmol l^{-1} (95% confidence interval 0.09, 0.43); the mean increase in serum sodium concentration was 1.49 (0.56, 2.43) mmol l^{-1} . These differences were statistically significant from baseline (paired *t*-test, $P < 0.01$). The diuretic therapy changes in all 30 patients had been maintained at follow-up 6–12 months postreview.

Cost analysis

Total time spent on the clinics was 275 pharmacist hours and five GP hours (for comprehensive medication review). Additional time spent on protocol development was approximately 17 pharmacist hours and four GP hours. Table 1 details the cost analysis for the combina-

tion diuretics review. The reduction in the cost of diuretic prescriptions for the reviewed patients was significant ($P < 0.01$, paired *t*-test).

Three out of 61 (4.9%) patients in this study had baseline serum potassium concentrations above the reference range. The sensitivity analysis for cost per hyperkalaemia case prevented by the intervention is also provided in Table 1.

Discussion

Although over 100 patients were identified, only 61 patients were eventually reviewed. This is a realistic reflection of the general practice setting. Almost half of all patients reviewed had their PSD discontinued with a mean fall in serum potassium of 0.26 mmol l^{-1} . The lack of adverse clinical sequelae showed that the protocol used was appropriate and that a large proportion of PSDs were being prescribed unnecessarily.

Apart from the theoretical future clinical benefits, the 39% reduction in diuretic costs following review was substantial and this result reflects the predictions made in the Audit Commission's 1994 report [10]. The cost savings resulting from the intervention were slightly greater than the costs of service provision, and assuming that the changes are maintained, these will continue to be realized annually whilst input costs will only be incurred once.

It is likely that the development and implementation of the protocol in the two practices has changed prescribing behaviour, resulting in the avoidance of routine initiation of combination diuretics. The ten patients who had their PSDs discontinued before the intervention may be due to including GPs in the initial protocol development. However, the development of a PSD formulary, education of GPs on appropriate use of PSDs, and inclusion of electronic reminders on the prescribing system may be required to ensure that future intervention of this nature is unnecessary.

This study was carried out in only two medical practices and consequently the generalizability of the results may be limited. Furthermore, without a nonintervention (control) group it is not possible to take into account natural discontinuations or confounding factors such as changes in diet. The use of a nonintervention group was considered, but the limited study population and unwillingness of the medical practitioners to exclude patients resulted in the final study design.

The use of only one pharmacist may reduce the reproducibility of the intervention. The model of employing a pharmacist within a medical practice is not universal and may affect patient response to requests for attendance and willingness to accept therapeutic changes.

Figure 1 Serum potassium concentrations before and after potassium-sparing diuretic (PSD) discontinuation. $\square$ Baseline (mean = 4.45 mmol l^{-1}); $\blacksquare$ Follow-up (mean = 4.19 mmol l^{-1}).

Table 1 Cost analysis.

Cost parameter	Costs excluding protocol development	Costs associated with protocol development	Costs including protocol development
<i>Service provision costs</i>			
Pharmacist time†	22.5 h→≤422	17 h→≤319	39.5 h→≤741
GP time‡	2 h→≤79	4 h→≤157	6 h→≤236
Additional blood tests§	91 tests→≤223	—	91 tests→≤223
Total	£724	£476	£1200
Cost per patient	£11.87	—	£16.90
<i>Cost savings (annual)</i>			
Baseline diuretic cost¶	£2241	£424*	£2665
Diuretic costs after study	£1368	£77*	£1445
Diuretic cost savings	£873	£347*	£1220
Cost per patient	£14.31	—	£17.18
Net cost of service	-£149	—	-£20
Cost per patient	-£2.44	—	-£0.28
<i>Cost per potential hyperkalaemia case prevented</i>			
Study incidence 4.9%	£242	—	£345
Incidence range 1–10% [6, 9]	£119–£1187	—	£169–£1690

*Refers to the ten patients who had their PSD discontinued by their GP during protocol development. †Based on average pharmacist time of 10 min for data collection, 5 min initial pharmacist appointment and for patients having their PSD discontinued 10 min follow-up time at a cost of £18.75 per hour. ‡Based on average GP discussion time of 2 min per patient at a cost of £39.26 per hour. §Costed using the standard charge to the practices by the local hospital pathology laboratory—£2.45 per test. ¶Based on Drug Tariff prices December 1997.

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