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Safety profile of repaglinide as used in general practice in England: results of a prescription-event monitoring study

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Abstract Repaglinide is a prandial glucose regulator indicated for management of type 2 diabetes. This post-marketing study used the observational cohort technique of prescription-event monitoring (PEM) to monitor safety of repaglinide prescribed in primary care in England. Patients were identified from dispensed prescriptions issued by general practitioners (GPs) between December 1998 and January 2001. Demographic and clinical event data were collected from questionnaires posted to GPs at least six months after the date of first prescription for each patient. The cohort consisted of 5731 patients [median age 60 (IQR 51–68), 49.9% male]. Event incidence densities (IDs) [no. 1st reports/1000 patient-months of exposure] were calculated for all events reported. The most frequently recorded clinical events in the first month were diarrhoea (ID_1 10.3), malaise/lassitude (ID_1 8.1) and nausea/vomiting (ID_1 7.9). The most frequently reported reason for stopping was 'not effective' (647), with the most common clinical reasons being diarrhoea (60), malaise/lassitude (55) and intolerance (54). One hundred and thirteen adverse drug reactions (ADRs) were reported, with the most frequently specified being diarrhoea (10), abdominal pain (10) and nausea/vomiting (9). We concluded that repaglinide is generally well tolerated when used in general practice in England and did not identify any serious unrecognised adverse events.

Key words Repaglinide • Type 2 diabetes • Prescription event monitoring (PEM) • Safety

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Introduction

Repaglinide was launched in the UK market in October 1998 [1]. It is an oral insulin secretagogue developed for the management of type 2 diabetes inadequately controlled by diet and exercise, and may be given alone or in combination with metformin. It acts as a prandial glucose regulator, intended to maintain glycaemic control, without the risk of hypoglycaemia or fasting hyperinsulinaemia, irrespective of number of meals in one day. It is metabolised by the liver and excreted in the bile, with very little being excreted via the kidneys. It can therefore be used in patients with renal disorders [2, 3].

Prescription-event monitoring (PEM) is a method of post-marketing safety surveillance of newly marketed medicines, and was established in England in 1980 [4]. PEM studies drug safety under the conditions of normal clinical use and is complementary to the 'Yellow Card' scheme of spontaneous reporting of adverse drug reactions (ADRs) to the UK Medicines & Healthcare Products Regulatory Agency (MHRA)/Committee on Safety of Medicines

(CSM). This study aims to examine the safety of repaglinide used in general medical practice in England as a treatment of type 2 diabetes, to quantify the incidence of adverse events that occurred in patients treated with repaglinide and to identify any previously unrecognised ADRs.

Subjects and methods

Patients were identified by means of dispensed National Health Service (NHS) prescription data supplied in confidence by the Prescription Pricing Authority (PPA) in England between December 1998 and January 2001. A 'green form' questionnaire was sent to the prescribing general practitioner (GP) approximately six months after notification by the PPA of the date of the first dispensed prescription for each individual patient. In PEM, the green form requests information on patient age and sex; indication for prescribing; dose; duration of treatment (including start and stop dates); reasons for stopping the study drug; and events that occurred after the drug was prescribed, including those considered by the reporting GP to have been an ADR. The term 'event' is defined as including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter in the patient's notes. Thus, in PEM the exposure data are derived from the original dispensed prescriptions for the drug being monitored and the outcome data are the events recorded by the original prescriber on the green forms.

Reported events are coded using the Drug Safety Research Unit (DSRU) event dictionary, a hierarchical dictionary arranged by system-organ class with selective 'Lower level' terms grouped together under broader 'Higher level' terms. Those questionnaires with no information provided are classified as 'void' and excluded from the study cohort and subsequent analysis, as there is no means of determining whether uncompleted forms indicated no reported events.

The data were examined to detect uncommon events and the green forms were reviewed. Selected cases were followed up for additional information to assess causality. Follow-up information was assessed for causality by a clinical research fellow at the DSRU, using the criteria of: temporality, pharmacological plausibility, clinico-pathological nature and exclusion of other causes. Causality was graded as being probable, possible, unlikely or unassessable [5].

Pregnancies (those that occurred during treatment and within three months of stopping repaglinide), any events of interest or particular concern with this drug, or considered medically important and where additional information was required, were followed up by sending additional postal questionnaires to the prescribing GP.

If no clear cause of death could be established from the green form, the DSRU sought further information to identify the certified cause of death.

This study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical Science in collaboration with the World Health Organization [6]. The method of study also complies with the Guidelines on the Practice of Ethics Committees in Medical Research Involving Human Subjects, as issued by the Royal College of Physicians [7] and Multi-Centre Research Ethics Committees Guidance Notes 2000 [8].

Statistical analysis

The response rate for the study was determined as well as a demographic description of the cohort. Prescribing indications (and contexts) were also described, along with adverse events attributed by GPs to repaglinide and reasons for stopping treatment.

Incidence densities (IDs) were calculated for first reports of all the events reported during treatment with repaglinide during a specified time period (t). The figures were expressed as ID per 1000 patient-months of treatment [9].

$$ID_t = \frac{\text{Number of reports of an event } \textit{during treatment} \text{ for period t} \times 1000}{\text{Number of patient-months of treatment for period t}}$$

IDs for events occurring in the first month of treatment (ID_1), during the second to sixth months of treatment (ID_2) and for events occurring during the overall treatment period (ID_A) were calculated. The difference between the ID_1 and ID_2 was calculated. The 99% confidence intervals around the point estimate were calculated to examine whether the event rate between the two periods was increasing or decreasing. If the 99% confidence limits around the point estimate of the difference between ID_1 and ID_2 did not include the null value and was positive, this indicated that the rate of events in the first month was significantly greater than that in months 2–6. This can be considered to be a signal of an adverse event associated with starting repaglinide.

Results

GPs returned 6651 (43.8%) of the 15 191 green forms posted. Nine hundred and twenty (14.0%) of the forms that were returned were classified as void because they did not contain any clinically relevant data. [Reasons included patient not registered (347), blank form (235), no record of drug (150).] Therefore useful information was available on a cohort of 5731 patients.

Of the 5731 patients, 2860 (49.9%) were male with a median age (IQR) of 60 years (51–67) and 2846 were recorded as females (49.6%) with a median age (IQR) of 61 years (50–69). Overall, the median age (IQR) was 60 years (51–68). The age was not specified for 2623 patients (45.8%).

The major indication recorded for patients treated with repaglinide was diabetes mellitus (68.4%), while the remaining indications included clinical contexts for prescribing such as hypoglycaemia previously, inadequate control on previous drugs and obesity. Indication was not specified in 1565 patients (27.3%), although it can probably be assumed to be type 2 diabetes, as this is the only licensed indication for repaglinide.

After six months 76.1% of the patients (3930) for whom it was recorded that treatment was continuing or that the

Table 1 Most frequent incidence densities (ID) ranked for repaglinide in order of ID_1 per 1000

Higher term description	N_1	N_2	ID_1	ID_2	ID_1–ID_2	99% CI		N_A	ID_A
						Min	Max		
Dose increased	158	232	31.35	10.73	20.62	13.94	27.29	593	12.21
Diabetes mellitus, hyperglycaemia	105	347	20.83	16.05	4.78	-0.90	10.47	692	14.25
Not effective	78	330	15.47	15.26	0.21	-4.79	5.21	656	13.51
Diarrhoea	52	38	10.32	1.76	8.56	4.80	12.31	118	2.43
Malaise, lassitude	41	40	8.13	1.85	6.28	2.93	9.64	106	2.18
Nausea, vomiting	40	33	7.94	1.53	6.41	3.11	9.71	91	1.87
Headache, migraine	31	25	6.15	1.16	4.99	2.09	7.90	78	1.61
Hypoglycaemia	30	31	5.95	1.43	4.52	1.64	7.39	82	1.69
Intolerance	27	28	5.36	1.30	4.06	1.33	6.79	59	1.21
Non-compliance	24	25	4.76	1.16	3.61	1.03	6.18	85	1.75
Hospital referrals no admission	22	63	4.36	2.91	1.45	-1.13	4.03	152	3.13
Pain abdomen	22	40	4.36	1.85	2.51	0.00	5.03	90	1.85
Dizziness	18	17	3.57	0.79	2.78	0.56	5.01	50	1.03
Respiratory tract infection lower	16	53	3.17	2.45	0.72	-1.50	2.94	125	2.57
Dose reduced	14	38	2.78	1.76	1.02	-1.03	3.07	78	1.61
Respiratory tract infection higher	14	72	2.78	3.33	-0.55	-2.71	1.61	148	3.05
Condition improved	13	17	2.58	0.79	1.79	-0.11	3.70	41	0.84
Dyspepsia	13	20	2.58	0.93	1.65	-0.26	3.57	61	1.26
Rash	13	22	2.58	1.02	1.56	-0.36	3.49	43	0.89
Distension abdominal	10	6	1.98	0.28	1.71	0.06	3.35	17	0.35

N_1, total number of reports of each event during the first month of treatment; *N_2*, total number of reports of each event during treatment in months 2–6; *ID_1*, incidence density for each event during the first month of treatment; *ID_2*, incidence density for each event during treatment months 2–6; *ID_1–ID_2*, arithmetic difference between ID_1 and ID_2; *99% CI*, 99% confidence intervals for ID_1–ID_2; *N_A*, total number of reports of each event during the total treatment period; *ID_A*, incidence density for each event for the total treatment period

date of stopping was given were still being prescribed repaglinide. It was unknown in 9.9% (565) of patients. 71.0% (3224) of the 4542 green forms that included an opinion about effectiveness reported it to be effective.

The clinical events reported with the highest ID in the first month of treatment were diarrhoea (10.32), malaise/lassitude (8.13) and nausea/vomiting (7.94). The most frequent IDs ranked for repaglinide are included in Table 1. The events that occurred significantly more often in the first month of treatment with repaglinide, compared to months 2–6, were diarrhoea, malaise/lassitude, nausea/vomiting, headache/migraine, hypoglycaemia, intolerance, non-compliance, abdominal pain, dizziness and abdominal distension. Most of the clinical events reflect those seen in the Summary of Product Characteristics (SmPC) for repaglinide either directly or as possible symptoms of hypoglycaemia.

Events recorded on green forms that were coded as an ADR to repaglinide numbered 111 events in 83 patients. Those that were recorded three or more times are shown in Table 2. The most frequently reported ADRs were reported as unspecified side effects in 17 patients, followed by diarrhoea (10), abdominal pain (10) and nausea/vomiting (9). One case was an interaction between repaglinide and xipimide causing hypokalaemia. Nine of these 111 events were documented on the green form as having been reported to the CSM. One case each of myocardial infarction, visual disturbance, drug interaction, hypokalaemia, decreased libido and deteriorated vision were reported to the CSM (not shown in table).

In 1772 (34%) patients, 2036 reasons were recorded by the GP for stopping repaglinide therapy. Those recorded 10 or more times are shown in Table 3. The most frequently reported reason for stopping was ‘drug not effective’ in 647 (11.2%) patients and the most common clinical reasons, excluding

Table 2 Most frequently reported adverse reactions to repaglinide

ADR (lower level terms)	Count	Reported to CSM
Unspecified side effects	17	–
Diarrhoea	10	–
Pain abdomen	10	1
Nausea	9	–
Headache	7	1
Gastrointestinal unspecified	6	–
Dizziness	5	–
Distension abdominal	4	–
Hypoglycaemia	4	–
Intolerance	3	–
Malaise	3	–
Rash	3	1

Gastrointestinal unspecified, gastrointestinal system event with no specific lower level term in the DSRU dictionary

Table 3 Most frequently reported reasons for stopping (Total in bold)

Higher term	Reason for stopping	Count
Not effective		**647**
	Not effective	647
Diabetes mellitus, hyperglycaemia		**488**
	Diabetic control impaired	415
	Hyperglycaemia	37
	Diabetes mellitus worsened	19
	Glycaemic control poor	16
	Diabetes mellitus	1
Hospital referrals no admission		**66**
	Hospital referrals	65
	Hospital referrals: cardiology	1
Non-compliance		**66**
	Non-compliance	66
Diarrhoea		**60**
	Diarrhoea	60
Malaise, lassitude		**55**
	Malaise	43
	Lassitude	12
Intolerance		**54**
	Intolerance	54
Nausea, vomiting		**52**
	Nausea	44
	Vomiting	8
Patient request		**49**
	Patient request	49
Hypoglycaemia		**45**
	Hypoglycaemia	45
Other drug substituted		**36**
	Other drug substituted	36
Pain abdomen		**32**
	Pain abdomen	32
Headache, migraine		**31**
	Headache	31
Condition improved		**21**
	Condition improved	21
Rash		**19**
	Rash	19
Dizziness		**18**
	Dizziness	18
Unspecified side effects		**18**
	Unspecified side effects	18
Weight gain		**16**
	Weight gain	16
Gastrointestinal unspecified		**15**
	Gastrointestinal unspecified	15
Non-formulary		**15**
	Non-formulary	15
Non-surgical admissions		**15**
	Hospital admissions	15
Dyspepsia		**13**
	Dyspepsia	9
	Heartburn	4
Distension abdominal		**10**
	Distension abdominal	10

those not indication related, were diarrhoea (60, 1%), malaise/lassitude (55, 1.0%) and intolerance (54, 0.9%).

Pregnancies

There were five pregnancies reported during the study period. On follow-up, one patient had Fraser syndrome diagnosed in pregnancy and had a stillborn baby at 26 weeks. There were three babies born with no abnormalities reported and for one pregnancy the outcome was not determined.

Deaths

There were 126 (2.2%) deaths reported irrespective of whether on or off treatment. Cause of death was not ascertained for 27 cases. Myocardial infarction was the most common reported cause (19) followed by pancreatic cancer (11). None of these deaths were reported to be due to repaglinide.

Hypoglycaemia

The Product Information states that, as with other hypoglycaemic agents, hypoglycaemic reactions have been observed with repaglinide. It records the incidence as rare (>1/10 000, <1/1000). There were 82 cases reported on the drug in our study (31 in month 1). These cases were not all followed up. Sixty-three of the reported hypoglycaemic events were known to be concomitantly on metformin. The SmPC also reports that "During post-marketing experience, cases of hypoglycaemia have been reported in patients treated in combination with meformin or thiazolidinedione". One case of hypoglycaemia with fit was followed up, but was unassessable, as no further information was received.

Follow-up of selected events

The lower terms for the events that were assessed as probably/possibly related to repaglinide are shown in Table 4.

Case histories

Rash

Three cases of rash were assessed as possibly and one as probably being caused by repaglinide due to temporality and dechallenge information obtained on follow-up. One case of eczema exacerbation in an elderly man was also considered possibly related. The eczema manifested as a

Table 4 Selected events assessed on follow-up as probably/possibly related to repaglinide use

Event	Number of cases assessed as probable/possible
Skin	
Rash	4
Eczema	1
Urticaria	1
Musculoskeletal	
Myalgia	1
Psychiatric	
Abnormal dreams	1
Central and peripheral nervous system	
Paraesthesia	1
Migraine	1
Eye	
Visual disturbance (one was same patient as impotence)	2
Cardiovascular	
Angina	1
Palpitations	3
Respiratory	
Epistaxis	1
Alimentary	
Irritable bowel syndrome	1
Increased liver enzymes	5
Metabolic and endocrine	
Impotence (same patient as visual disturbances)	1
Weight loss	1
Urological	
Renal function test abnormal	1

florid skin eruption on the trunk and legs and the patient also developed cellulitis of both legs. One case of urticaria in an 87-year-old man, which developed after seven months on treatment, was assessed as possibly being caused by repaglinide.

Visual disturbance

One case of a middle-aged female who experienced a visual disturbance after one month of taking repaglinide was assessed as possibly related and a further case of a middle-aged man who experienced blurred vision on the same day as starting repaglinide was assessed as being probably caused by repaglinide. (The same patient also experienced impotence on the same day as starting repaglinide, which was also assessed as being causally related).

Palpitations

One case of palpitations followed up was assessed as probably related to repaglinide in an elderly lady who experienced palpitations one day after starting repaglinide. She developed palpitations about 30 min after taking repaglinide and they lasted for 30–40 min. They resolved on stopping the drug. Two other cases of palpitations were assessed as possibly related.

Abnormal liver function tests

Five cases of abnormal liver function tests were assessed as being possibly causally related to repaglinide.

Discussion

This was an observational cohort study of the post-marketing safety of repaglinide. There was no interference with the decision of the doctors about which drug to prescribe for their individual patients, because the exposure data were obtained from all dispensed prescriptions for the drug in England. The study was therefore free of this potential selection bias.

The study included 5731 patients (mean of 8.47 months of exposure to repaglinide). Thus the data are likely to have substantially increased the recorded safety database of the drug used in the kinds of patients who receive the medication in 'real world' clinical practice. The study was of national proportions and systematic in that the entire cohort for whom prescriptions were available represented the first batch of patients prescribed repaglinide after its introduction into clinical practice in England. The method of PEM is capable of identifying ADRs that none of the participating doctors suspected to be caused by the drug. The ability to collect data on all events experienced by a patient during the study period permitted the search for new signals of events not suspected by GPs to be due to repaglinide. The typical six-month period of observation in PEM studies from dispensing a prescription to data collection using the green form provides ample opportunity for patients to consult and thus for events to be recorded by the GP. The methodology readily permits contact between the medical and scientific staff of the DSRU and the prescribing GPs. It thus allows for extensive follow-up and for additional data to be obtained for patients of special interest or those who have died.

PEM methodology facilitates collection of data on a wide range of patients with characteristics likely to be representative of the population at large. While data on co-morbidity and co-prescribing information are not systematically collected, they are obtained in the follow-up of selected events.

Response rate in PEM is on average 57.4% (for green forms over 83 previous studies). Selection bias should be considered as we do not know at present the characteristics of patients of doctors who do not respond and whether these patients experience similar rates of adverse events when compared to those patients of doctors who do return green forms [10]. While the response rate for this study was lower at 43.8%, it is still good for general practice postal surveys in general [11], particularly as GPs were not paid for completing green forms. A factor associated with PEM response rates has previously been shown to be the number of questionnaires sent to each doctor. Another issue that should be considered with PEM is that, in common with other methods of pharmacovigilance dependent on a third party for providing the data, it depends on the accuracy and thoroughness of the GPs when filling out the initial and follow-up forms. Under-reporting, including under-reporting of serious or fatal adverse events, is possible in PEM.

Information on reasons for stopping a drug prematurely are one of the strengths of PEM and provide a good insight into why either a patient or prescriber decided to stop the therapy being monitored – no causality is implied. The main reason for stopping was 'drug not effective', whereas the main clinical reasons included adverse events listed in the SmPC.

Our study also demonstrated that non-compliance was significant in the first month of use of repaglinide (85 reports of non-compliance on treatment, with 66 as the reason for stopping). Our findings may be an underestimate, as it is not possible to estimate the degree of compliance with the prescribed medication in observational studies. Clinical reasons for withdrawal from our study were reported as diarrhoea, malaise/lassitude and 'intolerance'. However, of those GPs who expressed an evaluation, 71.0% reported that repaglinide was effective. It is also of note that after six months 76.1% of patients for whom it was recorded that treatment was continuing or that the date of stopping medication was given were still being prescribed repaglinide.

The most commonly specified adverse reactions whilst on repaglinide in this study were diarrhoea, abdominal pain and nausea. All these events are listed in the SmPC

and events which occurred significantly more often in the first month of treatment with repaglinide, compared to months 2–6, were diarrhoea, malaise, nausea, headache, hypoglycaemia, non-compliance, abdominal pain, dizziness, condition improved and abdominal distension. Headache and dizziness may be considered as symptoms of hypoglycaemia. No serious unrecognised adverse events were identified.

A post-marketing safety study including a patient population of any patient with type 2 diabetes previously treated with diet alone or a single hypoglycaemic agent switching to repaglinide or a single sulphonylurea was conducted in the UK between August 1998 and December 2001 [12]. The study included 1900 patients (1425 on repaglinide and 475 on sulphonylurea), and included over 400 GPs. Subjects who were on more than one therapy for type 2 diabetes were excluded. The average age of subjects was 59.8 and 12.5% were over 75. Treatment-related adverse events were reported as dizziness, headache, diarrhoea, nausea, palpitations, weight gain, itching and sweating. Hypoglycaemia was reported as an adverse event, but the investigators found no significant difference between the subjects on repaglinide and those on sulphonylurea, and serious hypoglycaemic episodes were only reported in 0.3% of patients on repaglinide.

On review of the published literature, one case of leukocytoclastic vasculitis associated with repaglinide has been reported, [13] but there were no such cases reported in our study.

Repaglinide is a short-acting antidiabetic meglitidine and as a prandial glucose regulator, its effect is to maintain glycaemic control without the risk of hypoglycaemia or fasting hyperinsulinaemia, irrespective of number of meals in one day. Therefore it is of interest that hypoglycaemia was found to be significantly associated with starting treatment (although it is recognised as a possible adverse effect, as with all antidiabetic medications). A possible explanation for the hypoglycaemia associated with starting repaglinide is drug interactions, however PEM does not routinely collect data on concomitant medications (apart from in follow-up questionnaires). Subsequent to starting the study, there were five reports worldwide of hypoglycaemia in patients taking both repaglinide and gemfibrozil (Lopid) [14]. The combination is now contraindicated, and the SmPC has been amended accordingly [15]. We reviewed all cases of the event 'hypogylycaemia' and found none in our cohort that were reported to be concomitantly on gemfibrozil from the prescription data available to us (although we would not know if they had been issued on another prescription).

Repaglinide is completely metabolised in humans and *in vitro* studies have suggested that cytochromes P450 (CYP) 2C8 and 3A4 mainly contribute to its oxidative biotransformation. Gemfibrozil, a fibric acid derivative hypolipidaemic drug and an inhibitor of CYP2C8 (but not of CYP3A4), greatly increases (by about 8-fold) the plasma concentrations of repaglinide and prolongs its glucose-lowering effect.

The widely used antimicrobial drug trimethoprim is a selective inhibitor of CYP2C8 *in vitro* and a recent study has investigated the effects of trimethoprim on the pharmacokinetics and pharmacodynamics of repaglinide in healthy subjects and the influence of trimethoprim on the metabolism of repaglinide by human liver enzymes [16]. The conclusion from this study was that although the interaction did not significantly enhance the effect of repaglinide on blood glucose concentration at the drug doses used, the possibility of an increased risk of hypoglycaemia should be considered during concomitant use of trimethoprim and repaglinide in patients with diabetes. Of 82 patients reported as having hypoglycaemia in our study it is possible that a proportion may have concomitantly been taking trimethoprim. However of the 70 reports of urinary tract infection, none were reported as having hypoglycaemia on the green form.

There has also been one report in the literature of an interaction of repaglinide and the concomitant use of the fourth-generation fluoroquinolone gatifloxacin leading to severe hypoglycaemia [17]. No cases were identified in our study.

Repaglinide was the first prandial glucose regulator to become available in the clinical setting [18]. This post-marketing surveillance study shows that repaglinide is generally well tolerated when used in general practice in England. The number of selected events assessed as possibly related to repaglinide was small and no serious unrecognised adverse events were identified within the power of the study. No major safety concerns were identified in this study.

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References

1. Guay D (1998) Repaglinide, a novel, short-acting hypoglycaemic agent for type 2 diabetes. Pharmacotherapy 18:1195–1204
2. Massi-Benedetti M, Damsbo P (2000) Pharmacology and cli-

nical experience with repaglinide. Expert Opin Investig Drugs 9:885–898
3. – (2004) Nateglinide and repaglinide for type 2 diabetes? Drug Ther Bull 41:52–54
4. Shakir S (2002) Prescription-event monitoring. In: Mann RD, Andrews E (eds) Pharmacovigilance. John Wiley and Sons Ltd, UK
5. Shakir S (2004) Causality and correlation in pharmacovigilance. In: Talbot J, Waller P (eds) Stephens' detection of new adverse drug reactions, 5th Edn. John Wiley and Sons Ltd, UK, pp 329–343
6. CIOMS/WHO (2002) International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva
7. Royal College of Physicians of London (1996) Guidelines on the Practice of Ethical Committees in Medical Research Involving Human Subjects
8. – (2000) Multicentre research ethics committees guidance notes. Royal Colleges. Available from http://www.corec.org.uk/wordDocs/Guidance.doc
9. Freemantle SN, Pearce GL, Wilton LW, Mackay F, Mann RD (1997) The incidence of the most commonly reported events with 40 newly marketed drugs – study by Prescription-Event Monitoring. Pharmacoepidemiol Drug Safety 6[Suppl 1]:1–8
10. Templeton L, Deeham A, Taylor C, Drummond C, Strang J (1977) Surveying general practitioners: does a low response rate matter? Br J Gen Pract 47:91–94
11. McAvoy B, Kramer E (1996) General practice postal surveys: a question too far? BMJ 33:732–733
12. McDonough S (2002) NovoNorm SAMM Investigator's Meeting, Monte Carlo. Unpublished Data; by personal correspondence
13. – (2003) Repaglinide. First report of leucocytoclastic vasculitis: case report. Reactions 1:939:14.
14. – (2003) Repaglinide and gemfibrozil: risk of hypoglycaemia. Reactions 1:953:2
15. – (2003) NovoNordisk. Summary of Product Characteristics for NovoNorm. Ref
16. Niemi M, Kajosaari LI, Neuvonen M, Backman HJT, Neuvonen PJ (2003) The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. Br J Clin Pharmacol 57:441–447
17. – (2002) Gatiflaxin interaction: first report of an interaction with concomitant antihyperglycaemics leading to severe hypoglycaemia in elderly patients: case reports. Reactions 1:926:9
18. Owens D, McDougal A (2000) Repaglinide: prandial glucose regulation in clinical practice. Diabetes Obes Metab 2[Suppl 1]:S43–S48