REVIEW ARTICLE

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Statins and Pancreatitis

A Systematic Review of Observational Studies and Spontaneous Case Reports

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Contents

Abstract

Many anecdotal reports have suggested that therapy with HMG-CoA reductase inhibitors ('statins') can cause acute pancreatitis. We aimed to quantify the association between statins and pancreatitis and to classify the adverse effect under the dose, time, susceptibility (DoTS) system.

We searched for controlled observational studies that assessed the risk of pancreatitis in patients receiving statins. In order to identify case reports of statin-induced pancreatitis, we looked for reports published in scientific journals and manually reviewed reports within the Canadian Adverse Drug Event Monitoring System (CADRMP) database.

Two observational studies were identified and the data pooled together in a meta-analysis. This yielded an odds ratio of 1.41 (95% CI 1.15, 1.74) for the risk of acute pancreatitis in patients with a past history of exposure to statins. We also identified 20 published case reports and 33 spontaneous reports from the CADRMP database. These data showed that pancreatitis can occur at both high and low doses, with 12 cases developing pancreatitis at less than the dose equivalent of simvastatin 20mg daily. Statin-induced pancreatitis can occur at any time but seems to be very uncommon early on and more likely to occur after many

months of therapy. There does not appear to be a cumulative dose effect and increasing age does not appear to be a major susceptibility factor. These finding should help clinicians to better manage and diagnose patients who are at risk of statin-induced pancreatitis.

There are now numerous case reports where HMG-CoA reductase inhibitors ('statins') have been implicated in the pathogenesis of acute pancreatitis.[1-18] In contrast, the authors of a recently published observational study came up with the rather unusual suggestion that statins may actually have a protective effect.[19] Evidence from existing literature overviews seems to be of limited help – there have been two systematic reviews assessing the safety data of statins but pancreatitis did not appear to have been specifically evaluated in either review.[20,21] As this potential for a serious adverse drug reaction (ADR) creates considerable uncertainty among the large numbers of clinicians and patients who use statins, we aim to systematically clarify:

1. the quantitative and statistical link between drug and purported adverse effect, using data from controlled observational studies; and
2. the classification of the adverse effect under the new and innovative dose, time, susceptibility (DoTS) system.[22] Knowledge of the dose, time-course and patient susceptibility characteristics would be very helpful in devising strategies to manage and minimise the risk of the adverse effect.

1. Literature Search Methodology

This is a systematic review in two parts covering (i) controlled observational studies and (ii) case reports.

1.1 Controlled Observational Studies

We searched PubMed in April 2006 using the search terms 'pancreatitis' AND 'case-control' OR 'cohort'. To widen the scope, the search was supplemented by:

- retrieving the potentially relevant articles and repeating the search using the 'related articles' link. This search method in PubMed looks for any additional articles, which have similar medical subject heading (MeSH) terms, and keywords in the title and abstract;
- manually checking the reference lists of relevant studies; and
- using the Web of Knowledge Cited References list to identify any additional new data. This search method has been shown to be very useful for the identification of observational studies and may potentially reduce publication bias as the retrieved articles were found to be less likely to show a positive association.[23]

The only selection criteria used was that included articles had to be controlled studies that reported the relative risk or odds ratios of pancreatitis in patients receiving statins. No language restrictions were applied to the search.

1.2 Case Reports

We searched several databases and search engines (MEDLINE/PubMed, EMBASE, Scopus, Cochrane library, Google Scholar) using the search terms: 'statins', 'HMG Co-A reductase inhibitors', 'simvastatin' OR 'Zocor', 'pravastatin' OR 'Pravachol', 'rosuvastatin' OR 'Crestor', 'lovastatin' OR 'Mevacor' OR 'Altocor', 'atorvastatin' OR 'Lipitor', and 'fluvastatin' OR 'Lescol'; combined with the term 'pancreatitis' to identify all case reports. The references of all case reports were searched to identify additional case reports and checked their citations in the Web of Knowledge Cited References index were checked for additional reports.

Articles were checked and selected if they described any suspected, possible, probable or definite case report of pancreatitis attributed to any of the statins. All articles were evaluated using predefined criteria – age, sex, particular statin, duration of treatment, the possibility of reintroduction, strength of interaction, concomitant medication and clinical outcomes. Data were inserted into a table.

To avoid publication bias, we retrieved unpublished spontaneous reports from the Canadian Adverse Drug Reaction Monitoring Program (CADRMP), which is maintained by Health Canada.[24] This is the only English language regulatory authority database that allows easy, unrestricted web access to detailed adverse event reports, including drug history and patient characteristics. A manual review of individual suspected ADRs reported with any of the statins from 1965 to September 2005 was undertaken to identify all the reports of pancreatitis. This included 129 ADRs reported with pravastatin, 366 ADRs for rosuvastatin or Crestor®, [1] 388 ADRs reported with atorvastatin or Lipitor®, 224 ADRs reported with simvastatin or Zocor®, 17 ADRs reported with lovastatin, Mevacor® or Altocor® (none reported with fluvastatin). Those ADRs were selected if they included a report of pancreatitis with any of these statins. The relevant reports were abstracted into the data sheet using the following information: age, sex, duration of therapy, dose of statin, outcome of reaction and concomitant medications. It is worth noting here that the case reports did not always provide complete information on these parameters.

As there are a variety of statins in use, we normalised the data around a daily dose of simvastatin 20mg based on the standard dose conversion provided in the literature – simvastatin 20mg = atorvastatin 10mg = rosuvastatin 5mg = pravastatin 40mg = lovastatin 40mg.[25]

2. Data from Observational Studies

We found two case-control studies evaluating the risk of pancreatitis in patients exposed to statins. The first study was carried out by Lancashire et al.[26] using the UK General Practice Research database from 1989 to 1998. Cases in this study were identified using the *International Classification of Diseases* (ICD) codes for acute pancreatitis. For each case, three age- and sex-matched controls without the diagnosis of acute pancreatitis were selected from the same general practice. Prescription data for any previous statin exposure were obtained for all the cases and controls prior to the date of diagnosis of the case of acute pancreatitis; the author's main analysis was based on prescription of statin within 360 days of the adverse event.

The second study was conducted in Denmark using computerised records from hospital discharges and linking these up with population prescription registries in three Danish counties.[19] Cases were identified using ICD codes for acute pancreatitis in the hospital discharge registry from the late 1990s until December 2003. For each case, ten age- and sex-matched controls were selected from the same county. Prescription data for any statin exposure at any time prior to the index date of diagnosis were obtained for all the cases and controls.

From the two studies, we extracted the raw numbers of patients who had 'ever' rather than 'never'

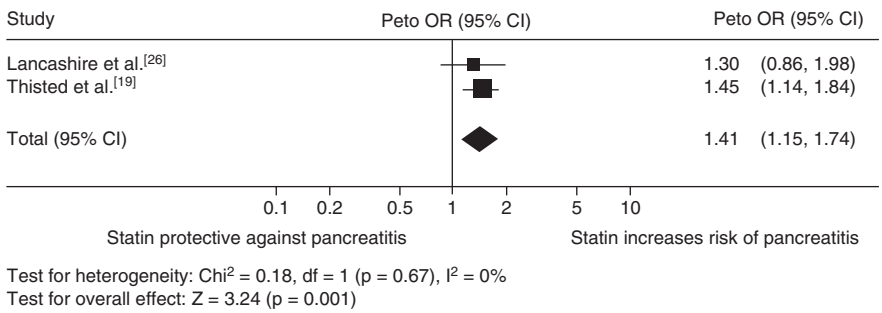

Fig. 1. Exposure to HMG-CoA reductase inhibitors ('statins') and risk of pancreatitis based on data from two observational studies.[19,26] **df** = degrees of freedom; **OR** = odds ratio.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. No. of reports of pancreatitis with statins based on data obtained from Canadian Adverse Drug Event Monitoring System database and published literature

Statin	No of case reports of pancreatitis (n = 53)
Atorvastatin	24
Rosuvastatin	10
Simvastatin	9
Pravastatin	4
Lovastatin	4
Fluvastatin	2

used a statin, prior to diagnosis. These data were pooled together with RevMan 4.2 in a meta-analysis using the Peto fixed effects model.[27] This yielded an odds ratio of 1.41 (95% CI 1.15, 1.74) for the risk of acute pancreatitis in patients who had consumed statins in the past year (figure 1). The I^2 statistic yielded a value of 0%, which indicates that little heterogeneity exists between the results from the two studies.

Interestingly enough, neither study found a significant relationship between drug use and the adverse event in a subgroup analysis of patients who had started on or received a prescription for statins 0–90 days before the diagnosis of acute pancreatitis. This may be because the subanalysis was based on a much smaller sample size and was not sufficiently powered to detect a significant link.

3. Data from Case Reports

There were 53 case reports available for analysis, of which 20 were published case reports and 33 were spontaneous reports identified in the CADRMP database (see table I).

3.1 Dose

Information on the statin dose was available in 46 cases. The frequency of pancreatitis across the dose range is illustrated in figure 2. This indicates that pancreatitis can occur at both high and low doses, with 12 cases developing at less than the dose equivalent of simvastatin 20mg daily. Efforts to avoid pancreatitis by using a low dose seem unlikely to succeed. Conversely, any patient presenting with signs or symptoms suggestive of pancreatitis should be fully evaluated irrespective of the dose of statin they are receiving.

3.2 Time (Duration of Therapy Prior to Adverse Reaction)

We were able to obtain the timing of the occurrence of pancreatitis after initiation of a statin in 28 patients (figure 3). Statin-induced pancreatitis can occur at any time, but seems to be very uncommon early on and more likely to occur after many months of therapy. The time course of the ADR is important here because most patients who take statins need to do so for the long-term control of hyperlipidaemia, and there is little prospect of limiting the treatment duration to avoid this ADR. However, the highest index of suspicion for the diagnosis of pancreatitis should be reserved for those patients who have been on therapy for months or years.

3.3 Dose and Time

There were only 28 cases available for analysis of the effect of dose and time, mainly because many of the reports did not state the duration of statin therapy prior to the adverse reaction. Figure 4 shows the dose in simvastatin equivalents against that of the time course.

The key points to note here are that even patients receiving low statin doses are susceptible to develop the adverse effect early on. Conversely, those on high-dose ranges were not particularly susceptible to developing the adverse reaction any earlier. This indicates that the adverse effect probably does not occur as a function of the cumulative ingested dose

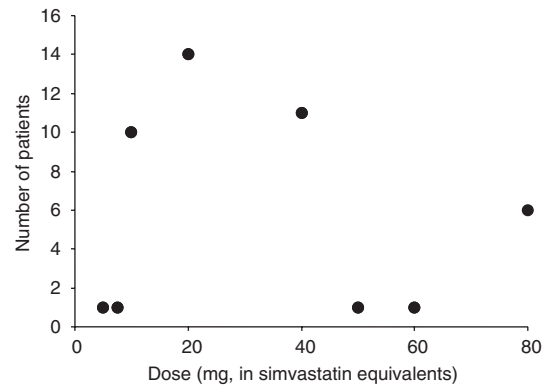

Fig. 2. Dose-relationship of HMG-CoA reductase inhibitors ('statins') to number of patients with pancreatitis. One patient on rosuvastatin 40mg (i.e. 160mg equivalence to simvastatin) has not been shown on the graph.

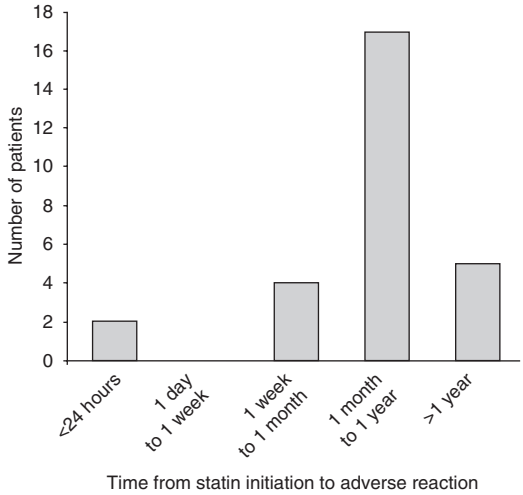

Fig. 3. Duration of HMG-CoA reductase inhibitor ('statin') therapy prior to adverse reaction.

and, based on figure 2 and figure 3, appears to be more related to the duration of treatment.

The absence of the dose-time response suggests that the reaction may be dose independent and unpredictable (type B) rather than dose dependent and predictable (type A).[28] Using the DoTS terminology, this means that the reaction neither occurs at supratherapeutic doses or subtherapeutic doses but instead is a collateral effect of statin use. Collateral effects include those "that occur due to a different pharmacological effect from the therapeutic action and those that occur through the therapeutic pharmacological effect but in another tissue".[22]

3.4 Susceptibility

3.4.1 Age

We were able to extract data on the age of the patients in 46 of the case reports. Their ages ranged from 36 to 86 years, with a median age of 58 years. Interestingly enough, there were only 8 of 46 (17%) patients who were >70 years; this is somewhat surprising as one would usually expect susceptibility to be higher in the older age groups. Moreover, coronary and cerebrovascular disease is more common in the elderly, thus necessitating the use of statins. There are two possible explanations here – one being that statins are relatively less frequently used in those aged >70 years, or the second being that the susceptibility to pancreatitis is not related to increasing age.

3.4.2 Severity of Pancreatitis

Pancreatitis with statins appears to be a mild reaction in the majority of cases and few deaths have been reported (n = 5). The majority of patients recover after cessation of the drug. The severity of pancreatitis was reported in only a few of the published case reports. In only one case[4] was the Atlanta system[29] used to classify the severity of pancreatitis. Some authors used the severity of the clinical presentation to classify the severity of pancreatitis but most published case reports (table II), as well as the spontaneous reports from the CADRMP database and the two case control studies,[19,26] did not provide any information on severity. However, the case-control study by Thirsted et al.[19] was based on hospital discharge records and we can infer that the pancreatitis was sufficiently severe for the patient to require hospital admission. Our assessment of the severity of pancreatitis is limited, but we can reasonably infer that statin-induced pancreatitis is usually benign in course in the majority of cases similar to other assessments of the course of drug-induced pancreatitis.[30]

4. Discussion

This systematic review indicates that statin therapy increases the risk of acute pancreatitis. However, pancreatitis is a relatively rare disease, with a quoted annual incidence varying up to 80 per 100 000 population.[32] The low level of underlying

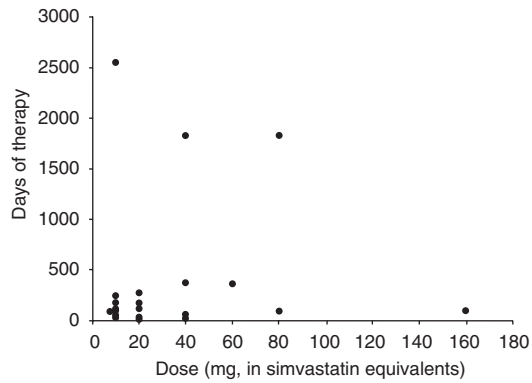

Fig. 4. Dose and duration of HMG-CoA reductase inhibitor ('statin') therapy prior to adverse reaction.

Table II. Severity assessment of the published case reports of statin-induced pancreatitis

Reports	Year of report	Age (y)	Sex	Drug regimen	Duration of treatment	Reintroduction	Outcome	Severity of pancreatitis
Pluhar[18]	1989	46	Male	Lovastatin 20mg bid	1 week	Yes; recurrence	Well	Mild pancreatitis
Ramdani et al.[15]	1991	40	Male	Simvastatin 10mg od	8 months	Yes; recurrence	Well	NK
Ramdani et al.[15]	1991	68	Male	Simvastatin 20mg	1 month	No	Well	NK
Couderc et al.[17]	1991	55	Female	Simvastatin 10mg od	3 months	No	Well	NK
Lons and Chousterman[16]	1991	50	Male	Simvastatin 20mg od	12 hours	No	Well	NK
Abdhul-Ghaffar and el-Sonbaty[14]	1995	55	Female	Lovastatin 20mg bid; gemfibrozil 300mg bid	2 months	No	Well	NK
Hunninghake et al.[31]	1998	NK	NK	Fluvastatin[a]	NK	NK	NK	NK
Wong et al.[13]	1998	73	Male	Lovastatin 20mg od; erythromycin[a]	7 years	Yes; no recurrence	Well	Severe
Belaiche et al.[12]	2000	63	Male	Atorvastatin 10mg od	8 hours	No	Well	NK
Tysk et al. [10]	2002	36	Male	Fluvastatin 40mg od	3 months	Yes; recurrence	Well	Mild
McDonald et al.[11]	2002	70	Male	Simvastatin 10mg od; fenofibrate[a]	6 months	No	Fatal	Severe

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Table II. Contd

Reports	Year of report	Age (y)	Sex	Drug regimen	Duration of treatment	Reintroduction	Outcome	Severity of pancreatitis
Miltiadous et al.[7]	2003	60	Male	Atorvastatin 40mg od; salicylates[a]	5 years	No	Well	NK
Anagnostopolous et al.[9]	2003	56	Male	Pravastatin 40mg od	6 months	Yes: recurrence	Well	NK
De and Nishioka[8]	2003	49	Female	Lovastatin 20mg	1 month	No	Fatal	NK
Singh et al.[5]	2004	71	Female	Atorvastatin 10mg; rosuvastatin 20mg	Several months (exact duration unknown)	Yes; recurrence	Well	Mild
Pezzilli et al.[6]	2004	64	Male	Simvastatin 20mg	6 months	Yes; recurrence	Well	Severe
Antonopoulos et al.[4]	2005	58	Male	Simvastatin 40mg; salicylate[a]	2 months	No	Well	Mild (using Atlanta system[29])
Kanbay et al.[3]	2005	86	Male	Atorvastatin 20mg; lisinopril 10mg	9 months	No	Well	NK
Becker et al.[2]	2006	60	Male	Pravastatin[a]	4 weeks	Yes; recurrence	Well	NK
Johnson and Loomis[1]	2006	58	Male	Simvastatin 10mg	4 months	Yes; recurrence	Well	Mild (although Ranson score = 4)

a Dose unknown.

bid = twice a day; **NK** = not known; **od** = once daily.

risk means that the number-needed-to-harm, based on an odds ratio of 1.41, is approximately 300 000 patients per year. Therefore, although pancreatitis with statins is likely to be real phenomenon, it is also something that the individual patient or clinician should not be too concerned about. Nevertheless, there are likely to be many millions of statin users on long-term therapy worldwide, which means that scores of patients will face the serious complication of acute pancreatitis.

Our efforts to classify this adverse reaction under the novel DoTS scheme also provide valuable information that correlates well with the case-control data. Thisted et al.[19] argued that new users (within 90 days) appeared to have a risk no different from controls and that there is no evidence of direct short-term toxic effects.This is borne out by our analysis of case reports, which showed that pancreatitis is much more likely to occur months or years into therapy.

4.1 Biological Mechanisms and Differences between Statins

The biological mechanisms of statin-induced pancreatitis have not been clearly elucidated. Nevertheless, the lack of a clear biological mechanism does not entirely eliminate the potential role of drugs in causing toxicity as even the drugs most strongly implicated in the causation of pancreatitis do not have a well explained biological mechanism.[33] On the other hand, statins are known to have pleitropic effects and the biological basis of the commonly recognised complication of statin use – rhabdomyolysis – is not entirely known. Mitochondrial toxicities and decrease in ubidecarenone (ubiquinone) levels have been postulated to cause rhabdomyolysis.[34] In some published cases, the authors believed that drug interactions may play a role.[3] Since most of the reports occur several months after statin therapy, an immediate hypersensitivity reaction is unlikely. Possible mechanisms could include an immune-mediated inflammatory response, a metabolic effect or direct cellular toxicity.[1] Interestingly, in animal models, statins have actually decreased the inflammatory mediators released during acute pancreatitis (interleukin [IL]-1β, IL-6 and tumour necrosis factor-α).[35]

Some researchers have suggested that there are differences in the safety profiles of the various statins and this may be related to their degree of inhibition of cytochrome P450 (CYP)A4 and their lipophilicity. A recent meta-analysis of statins attributed that the incidence of ADRs was higher with atorvastatin due to inhibition of CYPA4, with pravastatin being least likely to cause ADRs because it is not metabolised by CYPA4.[20]

In another case series reported by the US FDA of congenital malformation with statins, the relative hydrophilicity of pravastatin was attributed to explain the absence of congenital effects with pravastatin in comparison to other lipophilic statins, such as simvastatin or atorvastatin.[36] In our study, we found very few case reports of pancreatitis with pravastatin (n = 4). However, it is difficult to entirely explain this ADR based on the hydrophilic nature of statins, especially after several reports of pancreatitis occurred with rosuvastatin, another hydrophilic statin. Perhaps the relatively low number of case reports with pravastatin reflects the fact that it is used less frequently compared with other statins. The biological basis of this reaction needs further exploration in the laboratory, which is beyond the scope of our work.

4.2 Study Limitations

There are a number of major study limitations that need to be highlighted, particularly with respect to the analysis of case reports. First, it is impossible to be absolutely certain that the adverse event in any individual case report is indeed caused by the drug therapy. In view of this, we choose to use controlled data from observational studies as the means of statistically determining the association between pancreatitis and the statins. However, the available case-control studies do not provide any information on important characteristics of the adverse effect and it is only through the systematic review of individual reports that we can get some idea of the relationship to dose, time and other susceptibility factors.

One important limitation is that the cases reported in the journals and the CADRMP may not be representative of the typical patient. Authors may choose only to write up those cases that are special in some way and journal editors may select only

those that have substantial appeal to readers. We also do not know what biases may influence clinicians or other healthcare professionals to report a case to the CADRMP or not. Moreover, the adequacy of the case reports in terms of basic demographic details and drug history is often lacking. For instance, the age of a patient was not always available and we were seldom able to find out both the dose and duration of therapy together.

We did not have free access to detailed case reports from the other regulatory authority databases to be able to extract sufficient data to classify the adverse reaction under the DoTS scheme. This means that pharmacovigilance data are based on a Canadian population; however, by including published journal reports in our analysis, we aimed to broaden the applicability. Another limitation of the CADRMP is that these data should not be used for determining the incidence or estimating the risk of an ADR for a particular drug because they represent the observation of the individual health professionals and laypersons.

Although we have attempted to be systematic in our approach, the analysis was hampered by the lack of clinical detail or standardisation in both the journal case reports and the events reported to regulatory agencies. This is not a new problem – numerous deficiencies in ADR case reports were identified by Kelly[37] and there is an urgent need for CONSORT-style recommendations on the requirements for complete and standardised reporting.

Finally, the case-control studies may be susceptible to confounding by indication. For instance, hypertriglyceridaemia may be an important risk factor for pancreatitis; Thisted et al.[19] adjusted for this in their case-control study, whereas Lancaster et al.[26] did not. There may be other confounding factors that have not been elucidated yet: for example, we do not know if atherosclerotic vascular disease (for which the patients may require statins) has any effect on the risk of pancreatitis.

Given the potential weaknesses of the available evidence, the association between statins and pancreatitis could be better defined through a well conducted, prospective, cohort study.

5. Conclusions

Statin-induced pancreatitis appears to be a genuine adverse reaction but is of extremely low incidence and mild severity in the majority of cases. Many of the patients affected by the adverse effect were taking the statins at the lower dose ranges, equivalent to simvastatin ≤20mg daily. The adverse reaction seems to develop most commonly after months or years (i.e. more likely after long-term exposure) and can occur with all the statin drugs. These findings should help clinicians to better manage and diagnose patients who are at risk of statin-induced pancreatitis.

Future research should be aimed at overcoming specific gaps in the evidence, namely the exact magnitude and strength of the association between statins and pancreatitis as well as the precise causative biological mechanism. Such information will help to address the existing uncertainties and lead us to a better understanding of the adverse effect.

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