Pancreatitis During Drug Treatment: a Comparative Evaluation of Three Algorithms in Assessing the Causal Role of Drugs

Panrasri Khonputsa, B.Sc.(Pharm), M.Sc.,* Willem K. Amery, M.D., Ph.D., F.F.P.M.**
Leonard Kaufman, Ph.D.,*** Tony JJ Van Tittleboom, M.D., M.F.F.M.**

Abstract: *Background*. None of the methods proposed for assessing the possible role of a drug in causing adverse events (AEs) has been accepted as the gold standard because of differences in the criteria used and in the weighing of each criterion. Accordingly, each AE has certain characteristics that differ from the others' such as background incidence, clinical features, etiologies, prognosis, etc. We felt that each method should be appropriate for use in evaluating each major type of AEs. *Aim*. We wanted to compare three widely used causality algorithms (Naranjo's, Karch and Lasagna's, and the French Imputability system) and to find out which of them is more appropriate for assessing the causal role of a drug in cases of acute pancreatitis. *Materials and Methods*. 100 consecutive cases of pancreatitis in Janssen's AE database were assessed using the three algorithms; a Global estimate made by trained experts was used as a reference. The outcomes from the three algorithms were statistically compared using Wilcoxon's matched-pairs Signed Rank Test, Spearman's Rank Correlation Coefficient Test. P-values of less than 0.05 were considered significant. *Results*. We found significant differences and low correlation between each pair of algorithms ($r=0.27-0.59$, $p < 0.05$). The highest correlation was obtained from the comparison between the actual scores on Naranjo's algorithm and the Global estimate and the poorest correlation was obtained from the comparison between the French system and the latter. The results from Karch and Lasagna's algorithm were bound to be unrelated or conditional. Naranjo's algorithm yielded overall higher values than the Global estimate (1-level higher) suggesting a non-appropriate grouping of results by this method. *Conclusion*. Regarding the usefulness of the algorithms, it is conceivable Naranjo's algorithm is the best method in assessing pancreatitis cases given that the grouping of the scores into four qualitative categories are more revised.

บทคัดย่อ: **การศึกษาเปรียบเทียบ Algorithms ที่ใช้ประเมินบทบาทยาต่อการเกิดตับอ่อนอักเสบ**

ปัณรสี ขอนพุดซา ภ.บ., M.Sc.* Willem K. Amery, M.D., Ph.D., F.F.P.M. ** Leonard Kaufman, Ph.D. **Tony J.J. Van Tittleboom, M.D., M.F.F.M.**
*กลุ่มงานเภสัชกรรม โรงพยาบาลมหาราชนครราชสีมา **Janssen Research Foundation, International Pharmacovigilance Department, Turnhouseweg 30, B-2340 Beerse, Belgium ***Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussel, Belgium

เวชสาร โรงพยาบาลมหาราชนครราชสีมา 2541;22:145-51.

*Department of Pharmacy, Maharat Nakhon Ratchasima Hospital
**Janssen Research Foundation, International Pharmacovigilance Department Turnhouseweg 30, B-2340 Beerse, Belgium
***Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussel Belgium

มีการพัฒนาวิธีการประเมินบทบาทของยาต่อการเกิดอาการอันไม่พึงประสงค์ขึ้นหลายวิธีแต่จนถึงขณะนี้ยังไม่มีวิธีใด เป็นที่ยอมรับให้เป็นมาตรฐานเนื่องจากใช้เกณฑ์ต่างๆ กันไปและให้น้ำหนักแต่ละเกณฑ์ไม่เท่ากัน ในขณะที่อาการอันไม่พึงประสงค์แต่ละชนิดก็มีความแตกต่างกันในแง่อุบัติการณ์ สาเหตุ อาการแสดงทางคลินิก เป็นต้น อาจเป็นไปได้ว่าวิธีการประเมินหนึ่ง ๆ เหมาะสมกับอาการอันไม่พึงประสงค์บางชนิดเท่านั้น *วัตถุประสงค์* เพื่อเปรียบเทียบ algorithms ที่นิยมใช้โดยทั่วไป 3 ชนิด คือ Naranjo's, Karch and Lasagna's และ French Imputability system เพื่อดูว่าวิธีใด เหมาะสมที่สุดในการประเมินบทบาทของยาต่อการเกิดตับอ่อนอักเสบ *วัสดุและวิธีการ* ใช้ algorithms ทั้ง 3 ตัวมาประเมินรายงานผู้ป่วยที่เกิดตับอ่อนอักเสบ 100 รายแรก ที่รายงานสู่ Janssen's AE Database โดยเปรียบเทียบผลที่ได้กับผลการประเมินโดยผู้เชี่ยวชาญ โดยใช้สถิติดังต่อไปนี้คือ Wilcoxon's matched-pairs Signed Rank Test และ Spearman's Rank Correlation Coefficient Test ที่ระดับนัยสำคัญร้อยละ 5 *ผลการศึกษา* ผลที่ได้จากการประเมินทั้ง 3 วิธี แตกต่างกันและไม่ค่อยสอดคล้องกันอย่างมีน้อยสำคัญทางสถิติ ($r=0.27-0.59$, $p<0.05$) พบว่าวิธีการที่ให้ผลสอดคล้องกับผลการประเมินโดยผู้เชี่ยวชาญมากที่สุด คือ คะแนนดิบก่อนที่จะจัดกลุ่มระดับความน่าจะเป็นของ Naranjo's algorithm ในขณะที่ French Imputability system ให้ผลสอดคล้องน้อยที่สุด ส่วนผลจาก Karch and Lasagna's algorithm ติดอยู่ที่ระดับ unrelated หรือ conditional เท่านั้น ในภาพรวมผลการประเมินโดย Naranjo's algorithm ที่จัดกลุ่มแล้วสูงกว่าผลการประเมินโดยผู้เชี่ยวชาญ1-2 ระดับอาจชี้ให้เห็นว่าการแบ่งกลุ่มคะแนนเป็นระดับความน่าจะเป็นยังไม่ค่อยเหมาะสมนัก *สรุป* Naranjo's algorithm เป็นวิธีการเหมาะสมที่สุดในการประเมินบทบาทยาต่อการเกิดตับอ่อนอักเสบ แต่การแบ่งกลุ่มคะแนนเป็นระดับความน่าจะเป็น ควรมีการพิจารณาเพิ่มเติม

Each pharmaceutical company/each health authority adopts one or more methods to assess whether or not the adverse event (AE) in a specific patient is due to the products used when receiving an AE case report from health care professional, consumer or other individual via a local company, an affiliated company or from WHO.

There is no 'gold standard' for causality assessment of the potential causal role of a drug in the genesis of an AE because of differences in criteria used and in weighing of each criterion.[1,2,3] This leads to disagreement of results from assessor to assessor, method to method, company to company, and country to country. Accordingly, each AE has certain characteristics that differ from the others' such as background incidence, clinical features, etiologies, prognosis, and diagnostic procedures, psychogenic vs. organic nature as well as its reversibility. Therefore, each method should perhaps be appropriate for use in evaluating each major type of AEs. To our knowledge, there have been no studies that compare causality assessment algorithms in evaluating causal role of drugs in certain type of AEs.

Conceivably, three causality algorithms for the assessment of the causal role of a drug are relatively widely used. Two of the algorithms (Naranjo's, Karch & Lasagna's) are internationally known. The third algorithm is the French Imputability system which is the only one that has been adopted by a country as the official algorithm for assessing causality of AEs.

In the present study we aim to evaluate the usefulness of the three mentioned algorithms in evaluating the causal role of a drug in the genesis of acute pancreatitis and to find out what the important elements are in evaluating drug-induced acute pancreatitis.

Materials and methods

One hundred consecutive cases of pancreatitis accumulated from 1984 to 1997 in Janssen Research Foundation's international AE database were assessed using each of the three above algorithms as well as by a global expert's assessment (i.e. a global estimate). Only case reports indicated as being "pancreatitis" by reporters were selected for use in this study.

Naránjo's algorithm[4], Karch and Lasagna's algorithm[5], the French Imputability system[6] and the Global Assessment were used to evaluate all 100 cases. The Global estimate was performed by three trained medical pharmacovigilance experts who volunteered to independently assess a fraction of different AE case reports. A fourth expert physician, in addition, also assessed all AE cases; if his score differed from the other one, the case was discussed with the other evaluator and a consensus score was agreed upon. The Global estimate was used as a reference in this study because all assessors had been evaluating AE cases occurring during certain drugs treatment for some years. All of them were aware of the drug properties, background incidence, clinical features, etiologies, prognosis, and diagnostic procedures, psychogenic vs. organic nature as well as reversibility of pancreatitis.

Spearman's rank correlation coefficient test, Chi - Square test, Student t-test and Wilcoxon's matched-pairs Signed Rank Test were used where applicable.[7] P - values of less than 0.05 were considered significant.

Results

The average age of the patients in the study was 43.7 years and the modes were 45 and 55 years (5 patients per each). Thirty-five patients belonged to the 41-65 years age group. There were 5 males, 45 females and 5 patients whose sex was unreported.

The time difference between the date on which the drug was started and the date when signs or symptoms of pancreatitis were observed for the first time in this study ranged from 3 hours (< 1 day) to 1,095 days (average 110.81 days).

Table 1 Patient's characteristics

	No. of patients
Age (yr)	
0-10	4
11-20	6
21-40	30
41-65	35
>65	14
Unknown	11
Sex	
Male	50
Female	45
Unknown	5
Time to onset of pancreatitis (days)	
0-90	53
> 90	22
Unknown	25

Approximately half of the cases were assessed by the global estimate as possibly drug-caused (score=2) and only 4 cases were considered probably drug-caused (score=3). None was 'very likely' drugged related. The actual scores on Naranjo's algorithm ranged from -2 to 7 in this study, most of the cases fell in between the scores of 1 and 3. Median and mode were 2 and 2, respectively.

Seventy-five percent of cases were considered by Naranjo's algorithm as possibly drug-related. Results obtained from Karch and Lasagna's algorithm were either unrelated (47%) or conditional (53%) while the French Imputability system assessed 90% of the cases as 'dubious'. Outcomes generated by each method are shown in the following table.

Table 2 Outcomes generated by each method. The outcomes obtained from each method shown in the same rows do not imply the same levels of causal links.

Global	Naranjo's grouping	Karch & Lasagna	French
Doubtful	Doubtful	Unrelated	Unlikely
(44)	(11)	(47)	(8)
		Conditional	Dubious
		(53)	(90)
Possible	Possible	Possible	Possible
(52)	(75)	(0)	(1)
Probable	Probable	Probable	Likely
(4)	(14)	(0)	(1)
Very likely	Definite	Definite	Very likely
(0)	(0)	(0)	(0)

The correlation coefficients between each pair of methods ranged from 0.27 to 0.59, $p<0.05$ (Spearman's correlation coefficients). The Global Estimate correlated well with Naranjo's exact score ($r=0.59$, $p<0.001$) and somewhat less with Karch and Lasaga's ($r=0.43$, $p<0.001$) and with Naranjo's grouping ($r=0.42$, $p<0.001$). As to the algorithms, the French system correlated well with Naranjo's grouping ($r=0.59$, $p<0.001$). The correlation between the Global estimate and the French system was low ($r=0.27$, $p<0.05$).

Wilcoxon's matched-pairs Signed Rank Test was applied to study the differences between global vs Naranjo's grouping and French system vs Karch and Lasagna's algorithm. Both pairs of methods were found to differ significantly in their results ($p<0.05$).

The impact of sexes and ages on the causality results were also assessed. Only the results obtained from the assessment made by the experts (reference study) were analysed. The basic theoretical question behind a causality assessment is whether the AE is 'yes' or 'no' drug-related. In the present analysis, and in order to err on the false-positive side, we have assigned the 'yes' answer to the 'possible' and higher scales and assigned 'no' to the lower one. This implies that for the global estimate, i.e. the reference in this study, the results of 2-possible and 3-probable (there were no 4-very likely cases) were put into the 'yes' group and only 1-doubtful cases were put into the 'no' group. By doing so, we obtained 44 cases in the 'no' group and 56 cases in the 'yes' group below. There was no significant difference in drug-relatedness between males and females with pancreatitis (Chi square, $p>0.05$).

The mean age of patients having 'drug-related' pancreatitis was 47.5 years, against 39.1 years in those with a 'non drug-related' pancreatitis. This was a significant difference (t-test and Mann-Whitney U-Wilcoxon Rank Sum W Test, $p<0.05$).

Discussion

Drug-induced acute pancreatitis is a very rare event.[8,9] In addition, it cannot be distinguished from other types of pancreatitis.[10-33] Assessment of causality is

difficult if there is no information on dechallenge and rechallenge and when other possible etiologies, including concomitant drugs and concomitant diseases, are also present.[34,35] Dechallenge is a major indicator since the prognosis of pancreatitis should be good after stopping the drug.[34] However, it lacks specificity as most cases of pancreatitis tend to improve, regardless of their cause; in addition, in many patients all potentially offending agents are stopped simultaneously. Rechallenge is, most of the time, not ethically feasible because pancreatitis is a serious condition that can be fatal. The information of whether or not a particular drug has been claimed to cause pancreatitis is not always helpful either; in addition, for newly marketed drugs, no reliable information tends to be available in this regard. This is also the reason why the results from Karch and Lasagna's algorithm never exceeded 2-conditional in this study, even though the rechallenge was suggestive in some instances. This occurs because the second question of the algorithm relies heavily on the literature review. If the latter is negative (drug not claimed to cause pancreatitis), the answer is inevitably 'no'. Therefore, the final assessment is bound to be 'unrelated' or 'conditional'. Yet, drug causality can be possible, probable or very likely even if it has never been documented before that a particular drug can cause a certain adverse effect; dechallenge and rechallenge information deserve more weight in this context.

The Global estimate correlated best with the Naranjo's exact score. This may point to a superior accuracy of the latter method as compared to the other. However, Naranjo's grouping did not correlate well with the Global estimate. We found that Naranjo's grouping of results are globally higher than those from the global estimate as follows:

Global estimate < Naranjo grouping	43%
Global estimate = Naranjo grouping	55%
Global estimate > Naranjo grouping	2%

It is conceivable that the exact scores are not appropriately grouped for an evaluation of pancreatitis case. Twenty-two of the 28 cases with a total score of 1 (and therefore classified as 'possible') were considered 'doubtful' by the global estimate. In contrast, 28 of 35 cases with a score of 2 were considered 'possible' by the same estimate. This may suggest that for the evaluation of pancreatitis, a score of 1 fits better in the group of 'doubtful' cases. Five of 7 cases with a total score of 4 (and therefore classified as 'possible') were considered 'possible' by the Global estimate. Similarly, 7 of 11 cases with a score of 5 (classified as 'probable') were also considered 'possible' by the global estimate. This may suggest that, for the evaluation of pancreatitis, a score of 5 should fall in the 'possible' category. There were not enough cases to distinguish 'probable' from 'definite' (of 3 remaining cases, 2 cases with a score of 6 were classified as 'possible' and 'probable' respectively and 1 case with a score of 7 was classified as 'possible' by the Global estimate).

Conclusion

Regarding the usefulness of the three algorithms, the following tentative conclusions seem acceptable:

1. Especially for newly marketed drugs, Karch and Lasagna's algorithm has an important drawback because it relies too heavily on what is already known regarding the (new) drug's possible role in causing clinical cases of pancreatitis.

2. Naranjo's exact score showed the best correlation with the Global estimate made by the expert, but after these exact scores were grouped into the four qualitative categories, it appeared that the correlation lost much of its strength. This appears to be due, at least in part, to the position of the score '1' that is now grouped under 'possible' whereas 'doubtful' may be

more appropriate for the evaluation of a pancreatitis case. Similarly, the score of '5' seems to fit quite well in the 'possible' group rather than in the 'probable' one.

Acknowledgment

This work was part of a master thesis presented at the Master Program in Medical and Pharmaceutical Research, Vrije Universiteit Brussel, Belgium and was conducted at the Janssen Research Foundation, International Pharmacovigilance Department, Turnhoutseweg 30, B-2340 Beerse under the guidance and supervision of Dr. W. K. Amery as a promotor, Prof. Dr. Leonard Kaufman as a copromotor and Dr. Tony Van Tittelboom as a supervisor.

References

1. Strom BL. Pharmacoepidemiology 2. New York: Churchill Livingstone, 1994.
2. Michel D, Knodel L. Comparison of three algorithms used to evaluate adverse drug reactions. Am J Hosp Pharm 1986;43:1709-14.
3. Pere JC. Computerized comparison of six adverse drug reaction assessment procedures. Clin Pharmacol Ther 1986;40:451-9.
4. Naranjo CA, BustoU, Sellers EM, et al. A method for estimating the probability of adverse drug reaction. Clin Pharmacol Ther 1981;30:239-45.
5. Karch FE, LasagnaL. Toward the operational identification of adverse drug reactions. Clin Pharmacol Ther 1977;21: 247-54.
6. Begaud B, Evreux JC, Jouglard J, Lagier G. Unexpected or toxic drug reaction assessmen (imputation). Actualization of the method used in France. Therapie 1985;40:115-8.
7. Kirlwood BR. Essential of medical statistics. London: Blackwell Scientific Publications; 1996.
8. Trapnell JE, Duncan EHL. Patterns of incidence in acute pancreatitis. Br Med J 1975;2:179-83.
9. Corfield AP, Cooper MJ, Williamson RCN. Acute pancreatitis: a lethal disease of increasing incidence. Gut 1985;26: 724-9.
10. Gambill E. Etiology and mechanisms of pancreatitis. Pancreatitis 1973;50-82.
11. Geokas MC. Ethanol and the pancreas. Med Clin North Am 198 4;68:57-75.
12. Niederau C, Luthen R. Alkohol und pankreaserkrankungen. Z Gastroenterologie (Suppl 3)1988;2:60-74.
13. Moreau JA, Zinsmeister AR, Melton LJ, et al. Gallstone pancreatitis and the effect of cholecystectomy: a population -based cohort study. Mayo Clin Proc 1988; 63:466-73.
14. Steinberg WM. Acute pancreatitis-never leave a stone unturned. New Engl J Med 1992;326:635-7.
15. de Lalla F, Pellizzer G, Gradoni L, et al. Acute pancreatitis associated with the administration of meglumine antimonate for the treatment of visceral leishmaniasis. Clin Infect Dis 1993;16:730-1.
16. Marbet UA. Gallstone-associated acute pancreatitis: a field for endoscopic therapy. Dig Dis Sci 1992;10: 318-25.
17. Worning H. Etiologic aspects of chronic pancreatitis. Int J Pancreatol 1989;5:1-9.
18. Sibert JR. A British family with hereditary pancreatitis. Gut 1975;16:81-8.
19. Lashner BA, Kirsner JB, Hanauer SB. Acute pancreatitis associated with high concentration lipid emulsion during total parenteral nutrition therapy for Crohn's disease. Gastroenterology 1986;9:1039-41.
20. Bess MA, Edis AJ, Van Heerden JA. Hyperparathyroidism and pancreatitis. Chance or a causal association? JAMA 1980;24:246-7.
21. Izsak EM, Shike M, Roulet M, et al. Pancreatitis in association with hypercalcemia in patients receiving total parenteral nutrition. Gastroenterol 1980;7:555-8
22. Tromm A, Huppe D, Micklefield GH, et al. Acute pancreatitis complicating Crohn's disease: mere coincidence or causality? Gut 1992;33:1289-91.
23. Meltzer SJ, Korelitz BI. Pancreatitis and duodenopancreatic reflux in Crohn's disease. J Clin Gastroenterol 1988;10: 555-8.
24. Zuger A, Wolf B, El-Sadr W, et al. Pentamidine-associated fatal acute pancreatitis. JAMA 1986;17:2383-5.
25. Klar E, Rattner D, Compton C, et al. Adverse effect of therapeutic vasoconstrictors in experimental acute pancreatitis. Ann Surg 1991;214,:168-74.

26. Steinberg W, Tenner S. Acute pancreatitis. New Engl J Med 1994;330:1198-210.
27. Davis TV, Keeffe EB. Acute pancreatitis associated with acute hepatitis A. Am J Gastroenterol 1992;8:1648-50.
28. Bonacini M. Pancreatic involvement in human immunodeficiency virus infection. J Clin Gastroenterol 1991;13: 58-64.
29. Khuroo MS, Zargar SA, Yattoo GN, et al. Ascaris-induced acute pancreatitis. Br J Surg 1992;79:1335-8.
30. Bouteloup C, Michel P, Desechalliers JP, et al. Pancreatite aiguë récidivanteà Taenia saginatia. Gastroenterol Clin Biol 1992, 16:818-20.
31. Poisindex® Toxicologic Managements: Micromedex, Inc. 1974-1997.
32. Meier PB. Preventing ERCP-induced pancreatitis. Am J Gastroenterol 1992;87:1536-9.
33. Moulis H, Vender RJ. Pancreatitis after endoscopic cholangiography wihout pancreatiography. Am J Gastroenterol 1992;87:1888-9.
34. Delcenserie R, Grange JD, Laugier R, et al. Définition et critères d'imputabilité des atteintes pancréatiques aiguës méd icamenteuses. Gastroenterol Clin Biol 1992;16:761-3.
35 .Mallory A, Kern F. Drug-induced Pancreatitis Baillière's Clin Gastroenterol 1988:2:293-307.