

ORIGINAL RESEARCH

Pharmacologically pertinent period of effect (PPPE)

Melanie Suissa | Jacques LeLorier

Medical Student, Department of Medicine,
Université de Montréal, Montreal, QC, Canada

Correspondence

J. LeLorier, Pharmacoeconomic and
Pharmacoepidemiology unit, Centre de
recherche du Centre hospitalier de l'Université
de Montréal Tour St-Antoine, 850 St-Denis,
Montreal, QC, H2X 0A9, Canada.
Email: jacques.lelorier@umontreal.ca

Funding information

Canadian Institutes of Health Research,
Grant/Award Number: DSE-146021; Cana-
dian Network for Observational Drug Effect
Studies (CNODES)

Abstract

Background: The period of time during which a patient is exposed to a drug does not necessarily correspond to the period during which the drug produces the adverse effect under consideration. We propose the term Pharmacologically pertinent period of effect (PPPE) to address this time window. We explored the PPPE in light of the rofecoxib saga.

Methods: We identified the observational database studies of rofecoxib at doses 25 and 50 mg daily and thromboembolic events. We also obtained the Kaplan-Meier curves of Vioxx Gastrointestinal Outcomes Research trial (VIGOR) and Adenomatous Polyp Prevention on Vioxx (APPROVE) trials.

Results: We found seven observational studies with nine analyses. All the studies only looked at current exposure. At the dose of 25 mg, only three of nine analyses were barely statistically significant. At the dose of 50 mg, the risk ratios were much higher. The visual inspection of the Kaplan-Meier curves shows that in the APPROVE trial (25 mg), the placebo and rofecoxib curves start separating to become statistically significantly different only after 36 months. In contrast the VIGOR (50 mg), curves start separating very early and the divergence increases after 8 months.

Discussion: The 50 mg observational studies, looking at current exposure, correctively identified the almost immediate increase in risk evident in the VIGOR Kaplan-Meier curves. The absence of an immediate increase in risk shown by the APPROVE trial was also correctively identified by most observational 25 mg studies. To our knowledge no observational study was done on the long-term cardiac toxicity of the 25-mg dose. It would thus appear that the two doses of rofecoxib have different PPPEs.

KEYWORDS

exposure, misclassification, myocardial infarction, pharmacoepidemiology, pharmacology, rofecoxib, time windows

1 | INTRODUCTION

A policeman sees a drunk on his hands and feet under a streetlight.

Policeman: "what are you doing, sir?" Drunk: "I am looking for my car keys." Policeman: "where did you lose them, sir?" Drunk: "over there, in the park." Policeman: "why are you looking here?" Drunk: "because this is where the light is."

The cornerstone of a pharmacoepidemiological study is the classification of all the patients included in the study into one and only one

of four groups. Exposed-Event, Unexposed-Event, Exposed-No-event, and Unexposed-No-event. Misclassification of a significant number of patients will invalidate the measures of association produced by the study.

With respect to the outcome, the occurrence of the event of interest in a given patient is usually relatively straightforward given that there are clear-cut diagnostic criteria for most events of interest to pharmacoepidemiologists. If this is not the case, or if the necessary information to establish the diagnosis is not available in the database,

then perhaps the best solution might be to not do the study at all and do something else. There are fishes in them rivers.

With respect to exposure, however, the attribution of the status of exposed or nonexposed to the drug of interest is more intricate since it must be derived from the knowledge of the period of time during which the subjects took the drug. In database studies this information comes from prescriptions by physicians or dispensed prescriptions by pharmacists. For the purpose of this essay, we will assume that the information about the intake of the drug by the subjects is flawless. Unfortunately, it is often not the case. But that is another story.

The object of this dissertation is to emphasize the fact that the time span during which the drug is taken (or administered) does not necessarily match up with the period during which it produces the adverse event of interest to the study. We propose the term “pharmacologically pertinent period of effect” (PPPE) to define this latter time window. Continuous administration for some time might be necessary for the mechanism of action to kick in, while the pharmacological effect responsible for the adverse event may also be present after the drug has been discontinued.

We will present a series of examples where the duration of the drug exposure is clearly different from the time span of its deleterious pharmacological effect. We will then revisit the rofecoxib saga and try to better understand the results of the observational studies done at the time in light of the PPPE concept.

2 | EXAMPLES

In this section, we present a series of examples that illustrate the concept of the PPPE. In these examples, the PPPE is described in terms of its length of duration as well as its reversibility.

2.1 | Single use, immediate, reversible

Anaphylactic shock (Figure 1) can be instantaneous for both parenteral¹ and oral drugs² or occur within a couple of hours after the exposure. The relevant time has been described in a study as 1 hour for parenteral exposures and 2 hours for oral exposures.³ This example demonstrates a short PPPE. Thus, for parenteral drugs, the PPPE is 1 hour after the exposure, and 2 hours for oral drugs. This means that after these given time periods, the outcome cannot be attributed to the exposure. In other words, the outcome is only related to the exposure if it occurs within the PPPE.

2.2 | Single or continuous use, immediate, reversible

Ticagrelor (Figure 2) is an antiplatelet agent that reversibly binds to platelets to prevent platelet aggregation.⁴ Because its action is directly related to the concentration of drug in the blood (which depends on the pharmacokinetics of the drug), the effect begins shortly after the onset of treatment and stops quickly after discontinuation.⁵ Thus, the risk of bleeding (Figure 2) in patients taking ticagrelor is increased as soon as the treatment is started and goes back to normal once the drug is eliminated from the body.⁴ In this example, the PPPE is from

KEY POINTS

- The pharmacologically pertinent period of effect (PPPE) is an important element of pharmacoepidemiologic studies.
- It specifies the time period within which a specific outcome can occur as a result of a specific time window of exposure to a given dose of the drug
- With respect to the rofecoxib studies, the observational studies are consistent with two different PPPEs for the 25 mg and the 50-mg doses.
- At the dose of 50 mg, there are two PPPEs, one is the immediate thrombogenic effect and the other one is the delayed atherogenic effect.
- At the 25-mg dose, no immediate effect is seen, though we cannot rule out a long-term effect in the absence of duration analyses.

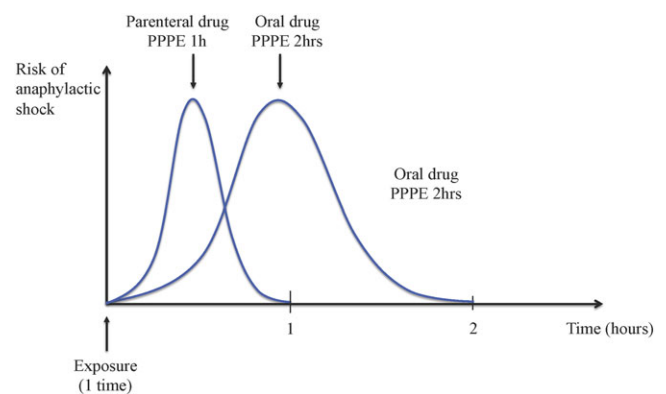


FIGURE 1 Instantaneous risk of anaphylactic shock after 1 time exposure to a parenteral or oral drug. PPPE: pharmacological pertinent period of exposure. Single use, immediate, reversible

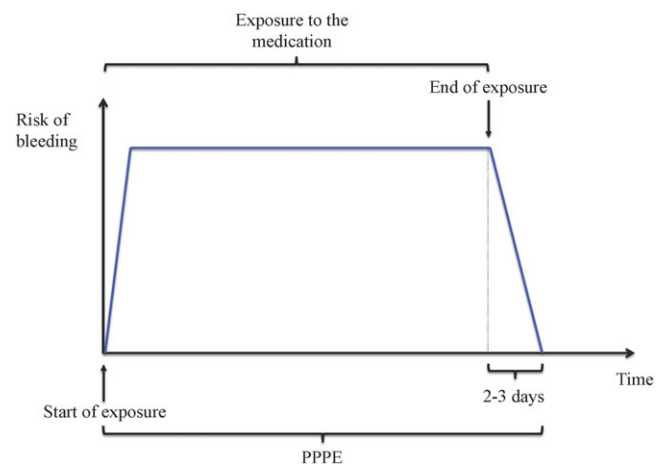


FIGURE 2 Risk of bleeding from continuous exposure to ticagrelor. PPPE: pharmacological pertinent period of exposure. Single or continuous use, immediate, reversible

the moment the treatment is started until about 2 to 3 days after the treatment is stopped (5 half lives).

Aspirin (Figure 3) is a classic antiplatelet drug that, unlike ticagrelor, irreversibly binds to platelets to inhibit platelet aggregation. This inhibition is initiated rapidly after the administration of the first dose.⁶ Similar to ticagrelor (Figure 2), the risk of bleeding caused by aspirin is increased instantly after onset of treatment. However, aspirin permanently inactivates platelets, which have a lifespan of 7 to 10 days in the circulation.⁷ Therefore, the risk of bleeding (Figure 3) remains for 7 to 10 days after the drug is stopped. At this point, the body has replaced the inhibited platelets with new platelets from the bone marrow.⁷ The PPPE in this example is from the initiation of treatment up until 7 to 10 days after the treatment is stopped. If only 1 dose is taken, the PPPE is 7 to 10 days.

2.3 | Continuous use, delayed, reversible

Hypertension (Figure 4) is one of the many adverse effects of long-term steroid therapy and is a result of sodium and water retention.

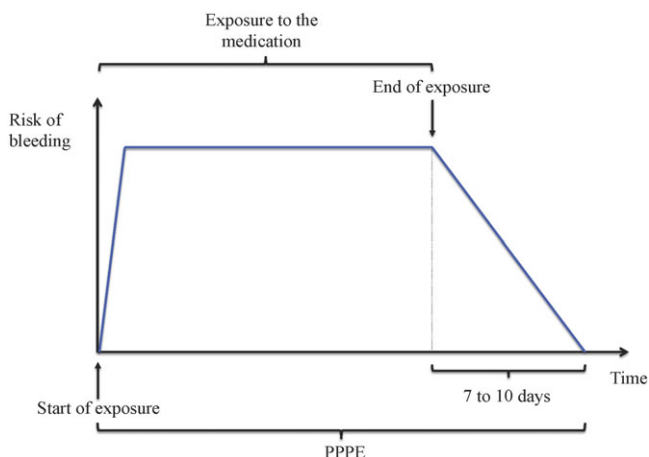


FIGURE 3 Risk of bleeding from continuous exposure to aspirin PPPE: pharmacological pertinent period of exposure. Single or continuous use, immediate, reversible

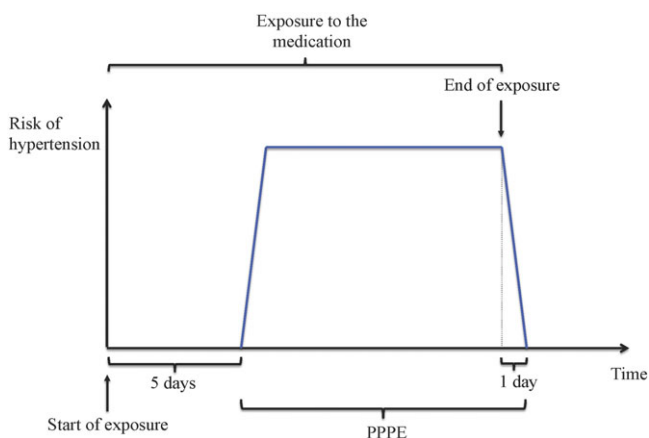


FIGURE 4 Risk of hypertension from continuous exposure to steroids. PPPE: pharmacological pertinent period of exposure. Continuous use, delayed, reversible

The risk of hypertension is directly related to the dose and duration of treatment.⁸ In a study by Sato et al, hypertension occurs only in patients receiving more than 20 mg of prednisolone daily.⁹ As shown in Figure 4, hypertension appears quickly after the onset of treatment. In a study by Williamson et al, blood pressure increases rapidly after 5 days of corticotherapy.¹⁰ Also, once the treatment is stopped and the drug is eliminated from the blood, the sodium and water retention resolve and the risk of hypertension goes back to its initial value (the effect is reversible). In this example, the PPPE begins 5 days after the onset of treatment and stops about 1 to 2 days after discontinuation. Therefore, if hypertension appears before 5 days of continuous treatment or after sporadic use, it should not be attributed to the corticosteroid.

2.4 | Single use, immediate, reversible

Chemotherapeutic drugs are known for their several adverse effects, cardiotoxicity being one of the more severe. Cardiotoxicity has been particularly well documented with anthracyclin-based chemotherapy. Acute anthracyclin cardiotoxicity is uncommon, reversible, and independent of the dose. It can occur instantly after initiation of therapy up to 2 weeks after the end of treatment.¹¹

2.5 | Continuous use, irreversible

In addition, chronic anthracyclin-induced cardiotoxicity can occur 1 year or more after the end of therapy and can lead to irreversible cardiomyopathy.¹² Some cases have been reported where cardiomyopathy appears several years after completing therapy.^{13,14} As shown in Figure 5, the risk of cardiotoxicity is existent from the beginning of treatment until death. It is unclear whether the risk remains constant, increases, or decreases with time.

2.6 | Delayed, irreversible

Vaginal adenocarcinoma (Figure 6) is rare and generally appears in women 50 years and older.¹⁵ In the 1960s, several cases of cancer of the vagina in girls 14 to 22 years of age were reported.^{15,16} A study by Herbst et al¹⁵ demonstrated that these cases were caused by

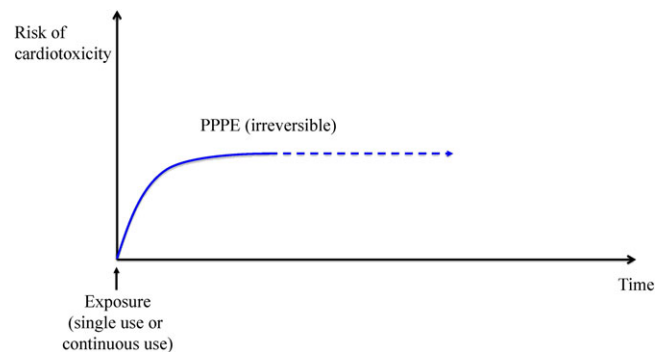


FIGURE 5 Risk of cardiotoxicity from exposure to anthracyclin-based chemotherapy. PPPE: pharmacological pertinent period of exposure. Delayed, irreversible

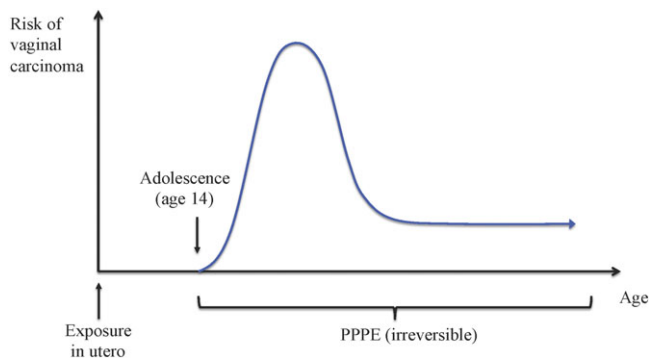


FIGURE 6 Risk of vaginal adenocarcinoma from exposition to diethylstilbestrol in utero. PPPE: pharmacological pertinent period of exposure. Delayed, irreversible

exposure to estrogens in utero. Diethylstilbestrol was commonly taken during pregnancy to prevent miscarriage.¹⁶ As shown in Figure 6, the risk of vaginal cancer caused by diethylstilbestrol exposure in utero appears at age 14, reaches a peak between ages 17 and 22,¹⁷ and then decreases after age 40.¹⁸ This means that the cancerous effect is irreversible. The PPPE for this example is the period of time between age 14 and death.

3 | ROFECOXIB SAGA

The rofecoxib saga, seen with the benefit of hindsight, provides an instructive example of the importance of the PPPE in the design of pharmacoepidemiologic studies. A quick review of the issue might be of interest for those who are too young to be around at the time or too old to remember.

The analgesic anti-inflammatory and antipyretic properties of acetyl salicylic acid were discovered in 1897.¹⁹ The ulcerogenic properties of this drug were rapidly recognized. In the 1960s, ibuprofen, the first nonaspirin nonsteroid anti-inflammatory (NANSAID), was marketed across the world.²⁰ A series of NANSAIDS were rapidly developed and made available to the patients. The aim of this flurry of activity was to obtain a share of this very profitable market but also to discover a drug that would have the benefits of the NSAIDs without their gastro-intestinal unwanted effects. ASA and NANSAIDS inhibit both COX-1 and COX-2 enzymes. Their beneficial effects are produced by the inhibition of the COX-2 mediated production of prostaglandin E₂. This substance produces inflammation, pain, and fever. Their toxic effects on the gastric mucosa are mediated by the inhibition of COX-1-mediated prostaglandin E₂.²¹ The activity was thus centered on discovering a selective COX-2 inhibitor. Rofecoxib was among the first of this class of drugs, which were labeled as Coxibs.

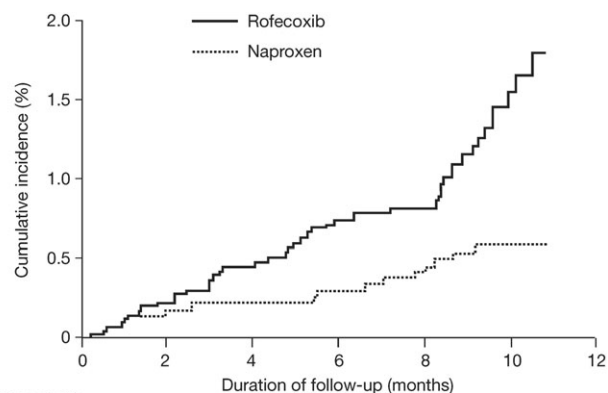
The Vioxx Gastrointestinal Outcomes Research trial (VIGOR)²² published in 2000 successfully demonstrated the gastrointestinal safety of rofecoxib (50 mg) when compared with naproxen and a similar relief of symptoms in patients with rheumatoid arthritis. However, once all the adverse events had been properly collected and adjudicated, there were significantly more cases of myocardial

infarction and stroke in the rofecoxib group (20 MIs with rofecoxib versus 4 MIs with naproxen).²³ The so-called dual hypothesis was proposed to explain this phenomenon.²¹ This hypothesis posited that the specific inhibition of the COX-2 enzyme might make patients more vulnerable to thrombotic disease and thus more likely to develop myocardial infarctions and strokes. In addition, this selective inhibition would also accelerate atherogenesis and increase blood pressure. These two mechanisms of action would thus result in two different PPPEs. The thrombotic effects would be immediate and require the presence of rofecoxib in the body. The atherogenic effects could only occur after prolonged and continuous exposure to rofecoxib.

The Kaplan-Meier curves of a serious thrombotic event in the VIGOR trial, in Figure 7, compare rofecoxib with naproxen. Visual inspection reveals that the curves separate early and that the divergence starts to accelerate at a later time point during the study follow-up. This would be consistent with the two components of the dual hypothesis operating simultaneously (an immediate thrombotic effect and a long-term atherogenic effect) at a dose of 50 mg of rofecoxib.

The pharmacoepidemiological community eagerly accepted the challenge, and a series of database observational studies explored the possibility of an association between rofecoxib and thromboembolic events.

In 2005, the Adenomatous Polyp Prevention on Vioxx (APPROVE)²⁴ trial was published. This double blind controlled trial recruited 2586 patients with intestinal polyps and randomized them to receive either rofecoxib 25 mg daily or placebo. The principal outcome was the recurrence of neoplastic polyps of the colon. Given the existence of the rofecoxib-thromboembolic events controversy, all the thromboembolic events were identified and properly adjudicated. The trial was discontinued 2 months ahead of schedule when the data and safety monitoring board reported a significant twofold increase in the incidence of serious thromboembolic events in the group randomized to rofecoxib 25 mg per day (46 thrombotic events with rofecoxib versus 26 with placebo). Subsequently, Merck, the



Number at risk	0	2	4	6	8	10	12
Rofecoxib	4,047	3,643	3,405	3,177	2,806	1,067	531
Naproxen	4,029	3,647	3,395	3,172	2,798	1,073	514

FIGURE 7 Kaplan-Meier estimates of the cumulative incidence of confirmed serious thrombotic events (with administration of 50-mg dose of rofecoxib) in the Vioxx Gastrointestinal Outcomes Research trial (VIGOR).

manufacturer of rofecoxib, withdrew the drug from the market. Careful inspection of the Kaplan-Meier curves (Figure 8) for thromboembolic events in the APPROVe trial leads us to conclude that the rate of events in the two groups remains virtually identical up to about 18 months of follow-up, after which point the two curves start to separate and become significantly different by 36 months. This visual inspection was confirmed by the nonproportionality of hazards ($p < 0.01$).²⁴ Thus, this trial provides no evidence of the immediate effect on coagulation, but it does provide evidence of a delayed effect in patients who take 25 mg rofecoxib regularly for prolonged periods of time. This delayed effect is compatible with the second component of the dual hypothesis, which posited that selective inhibition of COX-2 enzymes is atherogenic and produces hypertension. One would expect that it would take some time for an atherogenic effect to produce an increase in the rate of thromboembolic events. Indeed, the adverse event data from the VIGOR FDA report shows an increase in the rates of hypertension and cardiac heart failure.

Furthermore, a reanalysis of three trials of rofecoxib in Alzheimer's disease focusing specifically on cardiovascular events found similar results of increased risk.²⁵ These trials, conducted during the period 1998–2003, had reported no significant increase in cardiovascular deaths with rofecoxib (25 mg die) using an *on-treatment*

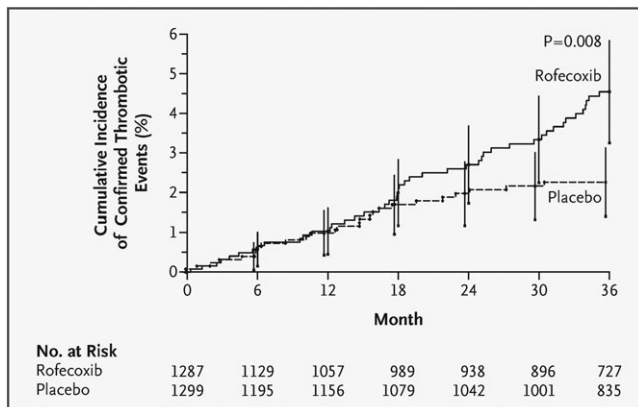


FIGURE 8 Kaplan-Meier estimates of the cumulative incidence of confirmed serious thrombotic events (with administration of 25-mg dose of rofecoxib) in the Adenomatous Polyp Prevention on Vioxx (APPROVe).

analysis of the data, which included events up to 14 days after drug withdrawal. The reanalysis performed intention-to-treat analyses, thus also included deaths occurring more than 14 days after drug withdrawal, and focused on confirmed cardiovascular deaths. The pooled results found a rate ratio of cardiovascular deaths of 3.57 (95% CI: 1.48–9.72; $P = 0.004$) with rofecoxib compared with placebo. The authors of the Intention to treat analysis concluded that: “if a drug has lingering effects or needs a latent period before an effect becomes evident, then an on-treatment analysis can provide only an incomplete picture of its toxicity.”

In view of these several results, it is of interest to review the observational database studies that were published on the subject with particular emphasis on the duration and doses administered. Since the rofecoxib arm of VIGOR was done with a dose of 50 mg daily and APPROVe with a dose of 25 mg daily, we focus on the observational database studies that specifically looked at the incidence of cardiovascular events at these specific doses. We used the study selection of a meta-analysis on myocardial infarction and NSAIDs.²⁶ Studies were included if they were observational cohort or case-control studies, if the NSAID was rofecoxib, if the comparator was no exposure or naproxen, and if the dose of rofecoxib was 25 or 50 mg. These studies are presented in Table 1. We observed that all the studies focus on current exposure to rofecoxib, though none reported the effects according to the duration of exposure, particularly prolonged exposure. Thus, these studies could not provide data on the delayed atherogenic effect observed in both the VIGOR and APPROVe trials. The studies suggested that the risk of cardiovascular events with low dose (25 mg) was not or barely significant while the risk with high-dose (50 mg) was significantly greater. This is consistent with the hypothesis of an immediate thrombogenic effect with a 50 mg dose but not with 25 mg.

4 | DISCUSSION

The PPPE is an important element of all pharmacoepidemiologic studies. It specifies the time period within which a specific outcome can occur as a result of a specific time window of exposure to a given dose of the drug. We presented a series of examples, which illustrate this concept. Arguably, most pharmacoepidemiological studies will focus

TABLE 1 Description of nine observational studies comparing high-dose (50 mg) and low-dose (25 mg) rofecoxib use and risk of myocardial infarction

Reference	Year	Database	Study Size	Exposure	Reference Group	Ratio (Low Dose)	Ratio (High Dose)
Ray et al ²⁹	2002	TennCare	453962	Current use	No use	1.03 (0.78–1.35)	1.70 (0.98–2.95)
Ray et al ²⁹	2002	TennCare	453962	New use	No use	1.02 (0.76–1.37)	1.93 (1.09–3.43)
Levesque et al ³⁰	2005	Health Insurance and NVSS	113927	Current use	No use	1.21 (1.02–1.43)	1.73 (1.09–2.76)
*Andersohn et al ²⁸	2006	GPRD	17561	Current use	No use	1.01 (0.74–1.40)	1.58 (1.16–2.15)
Garcia-Rodriguez et al ³¹	2008	THIN	716395	Current use	No use	1.41 (1.07–1.87)	6.50 (0.70–60.33)
Ray et al ³²	2009	GPRD	48566	Current use	Naproxen	1.44 (0.96–2.16)	2.29 (1.24–4.22)
Ray et al ³²	2009	GPRD	48566	Current use	No use	1.12 (0.90–1.41)	1.79 (1.07–2.97)
Varas-Lorenzo et al ³³	2009	Saskatchewan Health Care	364658	Current use	No use	1.61 (0.96–2.72)	1.24 (0.63–2.45)
Fosbol et al ³⁴	2010	Danish administrative registers	1028437	Current use	No use	1.32 (1.02–1.71)	3.02 (1.91–4.78)

*Study by Andersohn et al.²⁸ used a cutoff rofecoxib dose of <25 mg and ≥ 25 mg, therefore the high dose group includes 25 mg.

on current exposure that is the period of time during which the drug was in the patient's possession and will frequently not take into consideration the duration of the exposure. It is of interest to note that in most of our examples an analysis based on current exposure after short periods of time would have missed the association.

We interpret the results of our retrospective review of the rofecoxib saga as consistent with two different PPPEs for the 25 mg versus the 50 mg doses. At the dose of 50 mg, both components of the proposed dual hypothesis are present: the thrombogenic immediate and the atherogenic delayed effects. This was suggested by the spline curve of the Kaplan-Meier of all thrombogenic events in the VIGOR trial.²⁷ The PPPE appears early and the risk increases through time. The observational studies correctly identified this early increase in risk by using current exposure as the PPPE. The results of the APPROVE trial constitute the cornerstone of our retrospective review of the rofecoxib saga. This large, well-planned, and well-executed randomized double-blind trial is as close to the truth as we will ever get on the cardiovascular effects of rofecoxib at a dose of 25 mg daily. The Kaplan-Meier curves presented in Figure 8 of this study clearly show that they visually separate after about 18 months. And they become significantly different after 36 months.

There is an obvious lack of short-term effect. It is thus not surprising that the observational studies that explored the cardiovascular effects of a current exposure of 25 mg show inconsistent, mostly negative or barely positive results. We limited our review to observational studies that explicitly looked at doses of 25 and 50 mg because those were the doses used in the VIGOR and APPROVE trials. Furthermore, by comparing the results of these two doses within each study, we limited the impact of different methodologies. To our knowledge only one observational study explored the effects of long-term administration of rofecoxib.²⁸ When looking at continuous duration of current NSAID (rofecoxib) use, they found an increase in risk from 0.82 (0.56–1.19) for <3 months of treatment to 1.85 (1.32–2.59) for 3–12 months of treatment. However, in their analysis of continuous duration of use, the doses are not mentioned.

5 | CONCLUSION

The choice of the right PPPE(s) should be the object of a formal discussion early in the design of a pharmacoepidemiological study. All the information available on the drug-outcome relationship should be taken into consideration. The signal that triggered the study can provide valuable information. If it consists on case reports, the temporal association between the time window of the drug ingestion, its duration, and the time period of the reported events should dictate the choice of the PPPE. If the signal arises from a randomized controlled trial, Kaplan-Meier curves indicating the time to the event of interest would be extremely helpful. If the pharmacologic mechanism of the deleterious effect is known or suspected, it should also be taken into consideration.

Finally, what should we do when we do not know what to do? Most studies will focus on current exposure *because that is where the light is*.

ACKNOWLEDGEMENTS

Funded by the Canadian Network for Observational Drug Effect Studies (CNODES), a collaborating centre of the Drug Safety and Effectiveness Network (DSEN) is funded by the Canadian Institutes of Health Research (CIHR, grant no. DSE-146021).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Pick FJ, Patterson JF. Fatal anaphylactic shock due to penicillin. *Br Med J*. 1953;2(4836):605-606.
- Demirkan K, Bozkurt B, Karakaya G, Kalyoncu AF. Anaphylactic reaction to drugs commonly used for gastrointestinal system diseases: 3 case reports and review of the literature. *J Investig Allergol Clin Immunol*. 2006;16(3):203-209.
- International Collaborative Study of Severe A. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoepidemiol Drug Saf*. 2003;12:195-202.
- Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATElet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J*. 2011;32(23):2933-2944.
- Husted S, van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. *Cardiovasc Ther*. 2009;27(4):259-274.
- Flower R. What are all the things that aspirin does? *BMJ*. 2003;327(7415):572-573.
- Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol*. 1995;35(3):209-219.
- Fardet L, Kassab A, Cabane J, Flahault A. Corticosteroid-induced adverse events in adults: frequency, screening and prevention. *Drug Saf*. 2007;30(10):861-881.
- Sato A, Funder JW, Okubo M, Kubota E, Saruta T. Glucocorticoid-induced hypertension in the elderly. Relation to serum calcium and family history of essential hypertension. *Am J Hypertens*. 1995;8(8):823-828.
- Williamson PM, Kelly JJ, Whitworth JA. Dose-response relationships and mineralocorticoid activity in cortisol-induced hypertension in humans. *J Hypertens Suppl*. 1996;14:S37-S41.
- Adao R, de Keulenaer G, Leite-Moreira A, Bras-Silva C. Cardiotoxicity associated with cancer therapy: pathophysiology and prevention strategies. *Rev Port Cardiol*. 2013;32:395-409.
- Raschi E, Vasina V, Ursino MG, Boriani G, Martoni A, De Ponti F. Anti-cancer drugs and cardiotoxicity: insights and perspectives in the era of targeted therapy. *Pharmacol Ther*. 2010;125(2):196-218.
- Kumar S, Marfatia R, Tannenbaum S, Yang C, Avelar E. Doxorubicin-induced cardiomyopathy 17 years after chemotherapy. *Tex Heart Inst J*. 2012;39:424-427.
- Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *Jama*. 1991;266(12):1672-1677.
- Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med*. 1971;284(16):878-881.
- Nordqvist SR, Fidler WJ Jr, Woodruff JM, Lewis JL Jr. Clear cell adenocarcinoma of the cervix and vagina. A clinicopathologic study of 21 cases with and without a history of maternal ingestion of estrogens. *Cancer*. 1976;37(2):858-871.
- Melnick S, Cole P, Anderson D, Herbst A. Rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix. An update. *N Engl J Med*. 1987;316(9):514-516.

18. Verloop J, van Leeuwen FE, Helmerhorst TJ, van Boven HH, Rookus MA. Cancer risk in DES daughters. *Canc Causes Contr*. 2010;21(7):999-1007.
19. Sneader W. The discovery of aspirin: a reappraisal. *BMJ*. 2000;321(7276):1591-1594.
20. Bushra R, Aslam N. An overview of clinical pharmacology of ibuprofen. *Oman Med J*. 2010;25:155-1661.
21. Fitzgerald GA. Coxibs and cardiovascular disease. *N Engl J Med*. 2004;351(17):1709-1711.
22. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med*. 2000;343:1520-1528. 2 p following 8
23. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Bombardier et al., "Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis," *N Engl J Med* 2000;343:1520-8. *N Engl J Med*. 2005;353(26):2813-2814.
24. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*. 2005;352(11):1092-1102.
25. Madigan D, Sigelman DW, Mayer JW, Furberg CD, Avorn J. Underreporting of cardiovascular events in the rofecoxib Alzheimer disease studies. *Am Heart J*. 2012;164(2):186-193.
26. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, et al. Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf*. 2013;22(6):559-570.
27. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects--advantages and disadvantages. *Nat Clin Pract Rheumatol*. 2007;3(12):725-732.
28. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs and risk of acute myocardial infarction. *Circulation*. 2006;113(16):1950-1957.
29. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet*. 2002;360(9339):1071-1073.
30. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med*. 2005;142(7):481-489.
31. Garcia Rodriguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J Am Coll Cardiol*. 2008;52(20):1628-1636.
32. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes*. 2009;2(3):155-163.
33. Varas-Lorenzo C, Castellsague J, Stang MR, Perez-Gutthann S, Aguado J, Rodriguez LA. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. *Pharmacoepidemiol Drug Saf*. 2009;18(11):1016-1025.
34. Fosbol EL, Folke F, Jacobsen S, et al. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. *Circ Cardiovasc Qual Outcomes*. 2010;3(4):395-405.

How to cite this article: Suissa M, LeLorier J. Pharmacologically pertinent period of effect (PPPE). *Pharmacoepidemiol Drug Saf*. 2020;29(S1):61-67. <https://doi.org/10.1002/pds.4714>