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Statistics: Detecting a Rare Adverse Drug Reaction Using Spontaneous Reports

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More than 20,000 patients have been included in studies demonstrating the safety and efficacy of low-molecular-weight heparins (LMWHs) for postoperative venous thromboembolism (1). In May 1993, enoxaparin (Lovenox; Rhone-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, PA) was the first LMWH approved by the Food and Drug Administration (FDA) for general use in the U.S. In December 1997, the FDA issued a public health advisory to alert physicians and others that it had received more than 30 postmarketing reports of patients who had developed epidural or spinal hematomas with the use of LMWH and spinal or epidural anesthesia or spinal puncture (2). As of April 1998, a total of approximately 40 spinal hematomas were reported (3). The purpose of this report is to describe a statistical approach for identifying adverse drug reactions by using spontaneous reports and to describe the strengths and limitations of statistical analyses by using data from spontaneous adverse drug reaction reporting systems. The occurrence of spinal hematoma in association with neuraxial blocks in patients who received LMWH is used as an example.

Postmarketing Adverse Drug Reaction Monitoring

Pharmaceutical products undergo extensive testing and review before the FDA approves them for general use. However, even the most well-designed clinical trials cannot rule out the possibility of rare adverse events. Therefore, postmarketing surveillance is crucial for providing additional safety information that cannot be realistically collected before approval of the drug. The FDA maintains a database for spontaneous adverse drug reaction reports. Most of the reports received by the FDA originate from observations made by practicing physicians during the usual practice of medicine and are not derived from formal studies. Some observations are reported by practicing physicians directly to the FDA. However, most (80–85%) reports are made to the manufacturer who is then required by law to report the observations to the FDA (4,5).

The primary purpose of monitoring spontaneous adverse drug reaction reports is to generate preliminary signals that there may be a potential problem with a specific drug. The FDA's reporting system does not ensure complete capture of medication usage or adverse events and therefore cannot be used to generate incidence figures. Furthermore, for any given report, there is no assurance that the reaction was caused by the suspect drug. Rates calculated by using these data represent only reporting rates or the number of suspected adverse events given some overall estimate of drug exposure. However, in addition to generating signals of potential problems, the FDA's spontaneous adverse event database can be very helpful in identifying the types of reactions that may occur with a specific medication or group of medications, and in providing information on potential patient risk factors (6,7).

Statistical methods utilizing spontaneous reports have been proposed to aid decisions on the recognition of new adverse drug reactions and for signaling an increase in the frequency of adverse drug reactions over the course of time. Most of the statistical methods proposed involve a systematic comparison of the number of reports of a specific reaction in a recent time period to the number previously observed in a comparable time period or to the expected number of events in an unexposed population (8–12). These approaches are limited in their ability to detect a small shift or a slow trend in the reporting rate over time. For this reason, addi-

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tional methods have been suggested, including the use of cumulative sum and short memory techniques (12,13). For all of these statistical methods, estimates of drug exposure are required so that differential drug exposure during the comparative time periods can be taken into account. In most cases, the Poisson distribution is assumed to describe the number of adverse drug reaction reports observed in a given interval. Tubert et al. (8–10) describes a simple and straightforward approach for detecting new adverse drug reactions by comparing the number of reports during a specific time period to the number of coincidental occurrences that could be expected given the incidence of the event in the general population.

Statistical Approach

Consider a period of time during which a total of n patients have been treated with a given drug. If b is the background risk (i.e., incidence) for experiencing the event of interest in a similar but unexposed population, the expected number of coincidental occurrences among the treated patients during the period is nb. If drug treatment and the event of interest are independent, and all events are reported, the probability distribution of the number of reported events (X) approximates to a Poisson distribution with the parameter nb. The probability of observing x or more reported events, assuming independence of drug and event is:

$$\text{Prob}\,(X \geq x) = 1 - \sum_{k=0}^{x-1} e^{-m}\, m^k/k!, \text{ where } m = nb$$

For a given value of m, the test of independence between the event of interest and exposure to the drug is performed by limiting the risk of rejecting the hypothesis of independence (H_0) to a given value, α. If the number of reported events for the given time period ($x_{reported}$) is large enough such that $P(X \geq x_{reported}) \leq \alpha$, the hypothesis of independence is rejected and a signal is generated indicating a potential problem.

Tubert et al. (8) specifies three limitations associated with this approach. First, a signal does not indicate a causal relationship, only a statistical association that warrants further investigation. Second, the method is based on spontaneous reporting, which is known to only capture a small fraction of events. To compensate for this weakness, Tubert et al. (8) propose using a significance level larger than that usually chosen in statistical inference, although no specific alpha is recommended. Third, it can be difficult to estimate the background risk for the event of interest. Furthermore, the background risk in the general population may be different than that for patients likely to receive treatment with the given drug. Although not discussed, the third weakness could be reduced to some extent by extending the approach to incorporate age- and gender-specific incidence rates of the given adverse event in the general population, if these rates are available and if the age and gender distribution of the exposed population can be estimated. Even better would be to know the age- and gender-specific incidence rates for the given adverse event among people who would have indications for the medication use but were treated before the medication became available. Because the reporting rate is compared with the estimated incidence rate for the event in the general population, another disadvantage of this approach is that it requires an absolute estimate of the number of people taking the drug. Statistical methods that monitor the reporting rate by comparing consecutive time periods often use relative sales figures and do not require absolute estimates for the number of people exposed. These methods, however, only generate a signal if there is an increase in the reporting rate over time; no direct assessment is made to determine whether the reporting rate is higher than expected given the background risk for the event in an unexposed population for whom medication would be indicated, for example, spinal hematoma after spinal and epidural anesthesia in patients receiving LMWH.

Spinal hematoma is an extremely rare but very serious complication associated with spinal and epidural anesthesia. The actual incidence of spinal hematoma after neuraxial block is unknown. In a review of the literature between 1906 and 1994, Vandermeulen et al. (14) found only 61 published cases of an epidural or spinal hematoma involving neuraxial block techniques. Tryba (15), after evaluating 13 case series, including more than 850,000 patients who underwent an epidural block (only 3 of whom developed a spinal hematoma), estimated the risk for spinal hematoma after epidural anesthesia to be 1:150,000 (14). Similarly, after evaluating seven case series, including 650,000 subarachnoid blocks without a spinal bleeding complication, Tryba (15) estimated the risk for spinal hematoma to be 1:220,000 after spinal anesthesia (14). Because these rates are based on the upper limit of the 95% confidence interval, it has been generally accepted in the literature that the real incidence is less frequent (1,14,16–18).

By using 1:150,000 as the estimate of the background risk, Table 1 presents the probability of ob-

serving $\geq x$ spontaneous reports of spinal hematoma for a varying number of patients receiving LMWH and undergoing spinal or epidural anesthesia. For example, if 100,000 patients treated with LMWH underwent spinal or epidural anesthesia, the probability that 4 or more would develop spinal hematoma is .005 if the development of spinal hematoma and use of LMWH are independent (not associated). The probabilities presented in Table 1 assume that all adverse drug reactions are reported. If under-reporting occurs, the actual probabilities would be smaller than those presented.

In May of 1993, enoxaparin (Lovenox) became the first LMWH approved by the FDA for general use in the U.S. In 1995, the manufacturer submitted a revision of the package insert to increase the visibility and add clarity to the safety information regarding the use of enoxaparin and neuraxial anesthesia and postoperative indwelling epidural catheters. As of April 1998, there have been a total of approximately 40 reported cases of spinal hematoma associated with LMWH in patients undergoing spinal or epidural anesthesia (3). To assess the statistical significance of this finding, an estimate of the total number of patients who received enoxaparin and underwent spinal or epidural anesthesia during this time period is required.

Estimating the number of patients who receive LMWH and undergo neuraxial block is not a straightforward task. Not all patients treated with LMWH receive epidural or spinal anesthesia. Furthermore, the frequency of regional anesthesia is not consistent across all surgical procedures for which LMWH is used. For this reason, sales figures alone are not sufficient to estimate the number of patients that undergo spinal or epidural anesthesia with enoxaparin. One way to reduce the complexity of estimating the total number of patients at risk is to focus on a subset of procedures, such as total hip and total knee arthroplasty, that are likely to capture the majority of the exposed population. Because enoxaparin is the most widely used LMWH, accounting for nearly all of the LMWH usage in patients undergoing hip and knee procedures, the analysis has been restricted to this medication.

Table 2 presents the number of cases of spinal hematoma after spinal or epidural anesthesia with enoxaparin in patients undergoing total hip or total knee arthroplasty reported to the manufacturer as of April 1998 for the period from May 1993 to December 1997 (3). The manufacturer has estimated that in the U.S. approximately 201,000 patients taking enoxaparin underwent total joint arthroplasty using spinal (105,000) or epidural (96,000) anesthesia from 1995 to 1997 (FDA advisory committee, February 5, 1998). Of those undergoing epidural anesthesia, it is estimated that 37,000 had an indwelling catheter left in place postoperatively (FDA advisory committee, February 5, 1998). Because the number of exposed patients that underwent these procedures in 1993 and 1994 were not presented, these values were extrapolated by using the annual total sales information for the period from 1993 to 1997. Based on this extrapo-

Table 1. Probability of $\geq x$ Adverse Drug Reaction Reports of Spinal Hematoma Assuming a Background Risk of 1:150,000*

	No. of Patients Receiving LMWH Undergoing Neuraxial Block (in thousands)								
x†	10	25	50	100	150	200	250	300	500
1	.064	.154	.283	.487	.632	.736	.811	.865	.964
2	.002	.012	.045	.144	.264	.385	.496	.594	.845
3	<.001	<.001	.005	.030	.080	.151	.234	.323	.647
4			<.001	.005	.019	.046	.088	.143	.427
5				<.001	.004	.012	.028	.053	.243
6					<.001	.003	.007	.017	.121
7						<.001	.002	.005	.053
8							<.001	.001	.021
9								<.001	.007
10									.002
11									<.001

* Under the assumption that all occurrences of spinal hematoma associated with LMWH in patients undergoing spinal or epidural anesthesia are reported. If underreporting occurs, the actual probability of observing $\geq x$ reports would be less than that presented.

† The value of x represents the number of reported cases of spinal hematoma after neuraxial block in patients receiving thromboprophylaxis with LMWH. For a given number of exposed patients, the probability of observing $\geq x$ adverse drug reaction reports decreases as x increases. In the table, a specific probability is only given up to the point at which the probability of observing $\geq x$ reports is <.001. Although not presented, the probability would continue to decrease for larger x.

Abbreviation: LMWH, low-molecular-weight heparin.

Table 2. Number of Cases of Spinal Hematoma After Spinal or Epidural Anesthesia With Enoxaparin in Patients Undergoing Total Hip or Total Knee Arthroplasty Reported to the Manufacturer*

Type of Anesthesia	Year					Total
	1993†	1994	1995	1996	1997	
Overall	1	3	4	8	9	25
Regional anesthesia technique						
Epidural‡	1	2	4	6	4	17
Spinal§	0	1	0	0	2	3
Other unspecified‖	0	0	0	2	3	5

* As of April 1998, for the years from 1993 to 1997 (3).
† Enoxaparin was approved by the FDA for general use in May 1993.
‡ Of the 17 reported cases of spinal hematoma after epidural anesthesia, 14 were documented to have had an indwelling catheter that was left in place postoperatively (3).
§ These include two single doses and one continuous spinal technique (3).
‖ These include one unspecified technique, one unspecified continuous technique, and three general anesthetics after attempted spinal/epidural (3).

lation, it is estimated that there were approximately 234,500 patients who received enoxaparin and underwent total joint arthroplasty using spinal (122,500) or epidural (112,000) anesthesia from May 1993 to December 1997. Of those undergoing epidural anesthesia during this period, it is estimated that approximately 43,200 had an indwelling catheter postoperatively.

For the period from May 1993 to December 1997, there have been a total of 25 reported cases of spinal hematoma after spinal or regional anesthesia with enoxaparin in patients who underwent total hip or total knee arthroplasty. If the background risk for spinal hematoma is assumed to be 1:150,000, it is unlikely that more than 5 coincidental cases of spinal hematoma would be observed in a population of less than 300,000 exposed patients (Table 1). Therefore, there is strong evidence to suggest that the reporting rate for spinal hematoma is greater than 1:150,000 in this patient group.

The estimated reporting rates for spinal hematoma after spinal or epidural anesthesia with LMWH in patients undergoing total hip or total knee arthroplasty are presented in Table 3. Three of 25 reported cases of spinal hematoma summarized in Table 2 involved patients who underwent general anesthesia after attempted spinal or epidural anesthesia. These reports are not included in the calculation of the reporting rates because the number of patients who undergo failed needle placement is unknown. The overall reporting rate of spinal hematoma after spinal or epidural anesthesia with LMWH in patients undergoing total hip or total knee arthroplasty is estimated to be 1:10,700. There were 3 reported cases of spinal hematoma in patients who underwent spinal anesthesia (2 single dose and 1 continuous), resulting in an estimated reporting rate of 1:40,800. The overall reporting rate for epidural anesthesia (1:6,600) may be somewhat misleading because most of the cases involving epidural anesthesia

Table 3. Estimated Reporting Rate of Spinal Hematoma After Spinal or Epidural Anesthesia With Enoxaparin in Patients Undergoing Total Hip or Total Knee Arthroplasty

	No. of Events Reported*	Estimated No. of Exposures	Estimated Reporting Rate†	Estimated Reporting Rate per 100,000†
Overall	22	234,500	1:10,700	9.4
Spinal	3	122,500	1:40,800	2.4
Epidural				
Overall	17	112,000	1:6,600	15.2
With postoperative indwelling catheter	14	43,200	1:3,100	32.4

* Number of events reported as of April 1998 for the time from May to December 1993. Three reported cases of spinal hematoma involving patients who underwent general anesthesia after attempted spinal or epidural anesthesia are not included because the number of patients who underwent failed needle placement is unknown. Of the 22 cases included, 2 did not specify the anesthesia technique, 3 involved spinal anesthesia, and 17 involved epidural anesthesia. Of the 17 cases involving epidural anesthesia, 14 were documented to have had a postoperative indwelling catheter (3).
† Because of the underreporting of events and other potential biases inherent in the way reporting rates are calculated, these rates should be interpreted with caution (see text). They should not be interpreted as incidence rates.

were documented to have had a postoperative indwelling catheter. The subset of patients undergoing epidural anesthesia with a postoperative indwelling catheter have the largest estimated reporting rate (1:3,100).

It should be noted that the reporting rates presented in Table 3 represent the number of reported cases divided by a crude estimate of the number of treated patients undergoing spinal or epidural anesthesia. They do not represent incidence rates and should be interpreted with caution. As with all analyses of spontaneous reports, there are many limitations and potential biases that need to be carefully thought about before any decisions are made or actions are taken.

Potential Biases and Limitations of Reporting Rates

The potential biases that affect the reporting rates calculated from spontaneous reports of adverse drug reactions can be conveniently described in terms of those that influence the numerator (the number of events reported) and those that influence the denominator (the estimated number of patients exposed).

It is generally accepted that a major limitation of the use of adverse drug reaction data results from the under-reporting of events. It is not in the culture of U.S. medicine to notify the FDA about adverse events or product problems (19). Rogers et al. (20) found that of 418 physicians who indicated on a survey that they had detected a moderate-to-severe adverse drug event in their practice during the past year, only 76 (18%) reported the event to the FDA, drug manufacturer, colleagues, medical literature, or others. From a multivariate analysis, the likelihood of reporting an adverse event was found to be higher when forms were available, the event was not previously documented, the event was not considered a minor reaction, the physician had primarily an inpatient practice, and the physician's specialty was primary care, defined as internal medicine, pediatrics, or family/general practice (20).

The amount of under-reporting that occurs with adverse drug reaction monitoring is not constant over time and is known to be influenced by a number of factors. One of the primary factors influencing the number of adverse reactions reported for a given drug is the length of time the drug has been on the market. Historically, the number of adverse reaction reports for a given drug increases for the first 2 years after marketing and declines sharply thereafter, although there may be no evidence that the actual incidence of the adverse event has changed or that usage of the drug has declined. This phenomenon is often described as the "Weber effect" (7,21). Other external variables that influence the likelihood that a given adverse drug reaction gets reported to the manufacturer or the FDA include changes in the reporting system, changes in the package insert, recent publications in the medical literature, and mass media attention. A potential deterrent to reporting adverse events is the fear of involvement in litigation (22). In Rhode Island, Scott et al. (23) found that 8% of physicians responding to a survey indicated they would hesitate to report a suspected adverse drug reaction because of concern over legal liability. Similarly, Rogers et al. (20) found that in Maryland 3.1% of survey respondents would hesitate to report an adverse drug reaction because of the fear of increased liability. Other factors that influence the quantity and quality of data collected by spontaneous adverse event reporting systems have been discussed elsewhere (4,6,7,21).

In the case of spinal hematoma after neuraxial block with LMWH, many of these influences are relevant. Factors that would probably increase the reporting rate include the fact that the drug has only been on the market a short time, the event is very serious, and there have been publications in the medical literature discussing the controversial issue of neuraxial anesthesia in patients undergoing anticoagulation for surgery (1,14,16–18). There are other factors, however, that may deter a physician from reporting an occurrence of spinal hematoma, including the fear of legal liability and the fact that the potential for this adverse event is already documented on the package insert.

In addition to the biases that effect the likelihood of an observed spinal hematoma being reported, there are numerous potential biases that effect the estimate for the number of patients at risk. It is very difficult to estimate the number of people taking any specific drug in a given time period. In the case of spinal hematoma after spinal or epidural anesthesia in patients undergoing total hip or total knee arthroplasty with LMWH, these numbers were primarily based on estimates made by the manufacturer that were then extrapolated by using sales information to get estimates for the 1993–1997 time period. The methods and underlying assumptions used for the original estimates are unknown.

Because of the many biases inherent in the system for reporting spontaneous adverse drug reactions, it is not surprising that the usefulness of these data for research beyond signal detection is extremely limited. Although a signal may indicate a

potential problem with a specific drug, there are frequently many important questions that cannot be answered without further investigation. For example, the warning signal indicating that the frequency of spinal hematoma after epidural or spinal anesthesia is increased with the use of LMWH raises numerous questions.

Is the Signal Merely an Artifact Caused by a Poor Estimate of the Background Risk or a Poor Estimate of the Number of Patients Exposed? The background risk (1:150,000) was based on the frequency estimated by Tryba (15). Vandermeulen et al. (14) noted some of the limitations of Tryba's analysis, including the lack of information regarding patient characteristics. This makes it difficult to assess whether the background risk would be different for total joint arthroplasty patients who are judged to require thromboprophylaxis. There is also the possibility that the number of patients at risk has been underestimated. However, even if the background risk is assumed to be 1:35,000, and the number of patients exposed is assumed to be 350,000, it would be unlikely (P = .003) to observe 20 or more spinal hematomas. Therefore, it seems highly unlikely that the overall signal is merely an artifact.

Does a Cause and Effect Relationship Exist? The fact that a signal is generated does not necessarily indicate that a cause and effect relationship exists. Before inferring a causal relationship, there are many issues that should be considered, including among other things, the strength of the association, the biologic plausibility of the hypothesis, and the available experimental evidence (24).

Does the Lower Reporting Rate for Patients Undergoing Spinal Anesthesia Indicate That This Group Is Not at Increased Risk for Spinal Hematoma With LMWH? For patients undergoing spinal anesthesia, there were 3 reported cases of spinal hematoma in an estimated population of 122,500 exposed patients. If the background risk is assumed to be 1:150,000, there is evidence (P = .050) to suggest a potential problem. There were also three cases of spinal hematoma reported for patients who underwent general anesthesia after attempted spinal anesthesia. The significance of this finding cannot be assessed because the total number of patients who undergo general anesthesia after failed needle placement is unknown. It is important to remember that the generation of an alarm indicates the potential existence of a problem that should be investigated, it does not define the nature of the problem. Before the above question can be addressed, additional investigations need to be conducted to understand the mechanisms underlying the association between LMWH and spinal hematoma for patients undergoing spinal and epidural anesthesia.

Is the Risk for Spinal Hematoma After Spinal or Epidural Anesthesia With LMWH Higher Than the Risk for This Event After Spinal or Epidural Anesthesia With the Use of Other Anticoagulants? This is a very important question because the presence of anticoagulants at any time during neuraxial block has been considered critical in the formation of a spinal bleeding complication (14). For major orthopedic procedures, there are demonstrated benefits associated with thromboprophylaxis and many reasons for using LMWH. There are also advantages associated with using spinal or epidural anesthesia in this patient population. To make informed decisions regarding the choice of thromboprophylaxis and anesthetic technique, more information is needed on the comparative drug safety of the possible drugs for thromboprophylaxis and the various anesthetic techniques. Unfortunately, it is impossible to use spontaneous adverse drug reaction reports to adequately compare individual drugs because the biases that effect reporting rates for the drugs may differ in nature, order of magnitude, and direction (7,21).

Conclusion

Spontaneous reporting systems for adverse drug reactions play a very critical role in the postmarketing evaluation of drug safety. These systems are designed to monitor and detect rare adverse events. Statistical methods can be used to aid decisions on the recognition of new adverse drug reactions, and for signaling an increase in the frequency of adverse drug reactions over the course of time. However, spontaneous reporting systems are subject to numerous biases. For this reason, data collected via these systems cannot be used to generate incidence rates or to compare adverse drug reaction rates for different drugs. In the case of LMWH, there is strong evidence to suggest that the risk for spinal hematoma after neuraxial block is increased when compared with the background risk generally cited in the literature (1,14–18). It is unknown whether the risk for spinal hematoma after neuraxial block with the use of LMWH is higher than the risk for this event after neuraxial block with the use of other anticoagulants. Additional epidemiological studies (case-control studies or cohort studies) will be required to gain insight into many of the unanswered questions.

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