Epidémiol. santé anim., 1997, 31-32

USE OF THE CASE-CROSSOVER DESIGN IN VETERINARY EPIDEMIOLOGY : APPLICATION TO FATAL SKELETAL INJURIES OF RACEHORSES

Gardner I., Estberg L., Stover S.[1]

Le plan cas-croisé est une alternative aux études cas témoins lorsque l'on cherche à évaluer les effets transitoires des expositions aiguës sur le risque d'un événement aigu. Dans ce plan, chaque sujet (cas) est son propre témoin. Le risque relatif est estimé par la méthode de Mantel-Haenszel ou la méthode du maximum de vraisemblance. Le choix entre le plan cas-croisé et le plan classique cas-témoin dépend de l'importance des biais de sélection et d'information et de la possibilité de reconstituer l'historique de l'exposition pour chaque cas. Pour montrer l'intérêt de ce type de plan, nous l'avons appliqué sur les accidents observés chez les chevaux de course. L'étude a été planifiée pour évaluer l'association entre l'entraînement excessif des chevaux (mesuré comme un taux moyen de la distance cumulée excédant le $75^{ème}$ percentile pour chaque âge) et le risque d'une fracture osseuse fatale durant les 30 jours suivants. Le risque de fracture (tous types confondus) durant une période d'exercice à grande vitesse est augmenté par un facteur de 4.7 (IC à 95% : 3,2-6,9). Pour cette étude, l'approche cas-croisé est préférable à l'approche classique cas-témoin parce qu'il est difficile d'obtenir les témoins appropriés pour les cas de fracture qui apparaissent durant une course.

INTRODUCTION

For evaluation of a new treatment in human beings, a randomized crossover design often is used with alternation of each patient between the drug under test and a placebo or standard therapy. The method assumes no carry-over and period effects on treatment outcomes. Treatment sequencing and patient assignment are other important considerations. The observational equivalent of the randomized crossover design is the case-crossover design. The method was first described by Maclure (1991) to assess the effects of transient exposures on the risk of onset of acute events such as myocardial infarction. Recently, the case-crossover design was used to study urban traffic and child pedestrian injuries (Roberts et al., 1995). In a case-crossover design, each case provides its own control information. This design is especially suited to studies of transient exposures on acute events in which selection of appropriate controls is difficult or impossible. Subjects crossover between periods of transient exposure or non-exposure to the risk factor; this crossover, however, is not determined by the investigator and is assessed retrospectively from records or interview data. Each study subject (case) constitutes a separate stratum and provides its own self-matched control information in the form of «typical» exposure frequency. Control subjects and control strategies for time invariant confounders (among-subject confounding) are not necessary to estimate relative risk. In practice the method is more difficult to implement than a case-control study as it requires detailed information on the «usual» behavior/exposure pattern of each case. To our knowledge, the case-crossover design has not been previously used in veterinary epidemiology, although we believe that the method may have varied applications in this discipline.

METHODS

We used a case-crossover design to investigate the role of high exercise intensity in fatal skeletal injuries in Thoroughbred racehorses that died during racing and race training in California. Methods are described in detail in Estberg et al. (1997). Briefly, case horses (those with fatal skeletal injuries that occurred in 1991 or 1992) were identified through necropsy records of the California Horse Racing Board Post Mortem Program and their racing and training histories were reconstructed from a commercial racing history database. Exercise intensity was measured as the average rate of distance accumulation while racing and training during a 60-day sliding window. Exercise intensity was categorized as «high» (exposed) if it exceeded the 75th percentile for the year- and age-specific cutoff values, otherwise as non-exposed. Histories were partitioned into hazard periods (30 days immediately following the period of high exercise intensity) and non-hazard periods (remaining career days up to the date of injury excluding lay-up periods from races and official timed workouts of ≥60 days). A hazard period of 30 days was selected based on biologic criteria (Jones et al., 1989; Estberg et al., 1995). The Mantel-Haenszel pooled estimator (Rothman, 1986; Maclure, 1991) for a uniform incidence rate ratio (RR) and a 95% confidence interval (CI) was used to determine whether high exercise intensity increased the risk of fatal skeletal injury. Separate analyses were done for all skeletal injuries combined and for specific fracture types.

[1] Departments of Medicine and Epidemiology, and Anatomy, Physiology and Cell Biology, School of Veterinary Medicine, University of California, Davis, CA 95616, USA.

Exposure Status

	+	-	
Horse	a_i	b_i	
Horse-time	N_{1i}	N_{0i}	T_i

$$RR = \frac{\sum a_i N_{0i} \div T_i}{\sum b_i N_{1i} \div T_i}$$

where:

i	=	horse (case)
a_i	=	1 if injury occurred during a hazard period (exposed)
	=	0 if injury occurred during a non-hazard period (unexposed)
b_i	=	1 if injury occurred during a non-hazard period (unexposed)
	=	0 if injury occurred during a hazard period (exposed)
N_{1i}	=	hazard days
N_{0i}	=	non-hazard days

RESULTS

Two hundred and fourteen horses had catastrophic musculoskeletal injuries (193 skeletal fractures with or without ligamentous rupture; 21 ligamentous rupture only) during 1991 and 1992. The most frequent skeletal injuries involved the proximal sesamoid (n=73) and the third metacarpal (n=55) bones. For all fatal skeletal injuries combined, there was an increased risk (RR=4.7, 95% CI = 3.2 to 6.9) among horses with histories of high exercise intensity. This increased risk was also evident when horses with proximal sesamoid fractures (RR=4.2, 95% CI = 2.5 to 7.1) and third metacarpal fractures (RR = 11.3, 95% CI = 4.3 to 29.9) were considered separately.

DISCUSSION

Our findings using the case-crossover design were consistent with those of previous studies for fatal skeletal injuries that included control subjects (Estberg et al., 1995; Estberg et al., 1996). The primary advantage of the case-crossover design was that we were able to include training-related injuries that make up nearly 50% of all the racetrack injuries. Selection of appropriate training controls is difficult and may introduce confounding by previously described risk factors such as age, sex and horse quality. It is important to note that horses were only included in the study if they had raced or worked consecutively for ≥30 days prior to the outcome of interest. Relatively small numbers in strata limited our ability to adequately investigate modifiers of the relationship between high exercise intensity and fracture risk.

High exercise intensity (exposure of interest) was coded as a dichotomous variable based on categorization of continuous data (average rate of distance accumulation) above an arbitrary threshold (75th percentile values on an age- and year-specific basis). We assumed that once the threshold was exceeded, 30 days of elevated risk followed. Average latency periods of up to 1 month in length seemed plausible in light of prior studies which reported high running distances within 1 month prior to athletic injury (Jones et al., 1989; Estberg et al., 1995). Maclure (1991) has suggested an alternative approach which selects the appropriate hazard period as the one that maximizes the relative risk estimate. We have used this approach in a recent study of lay-up from racing of ≥60 days as a risk factor for humeral and pelvic fractures in racehorses (Carrier et al., 1997). In the present study we did not do a sensitivity analysis of different hazard period lengths primarily because the many different fracture types and the possibility that the appropriate hazard period might have differed by fracture type (especially cortical bone fractures versus cancellous bone fractures).

Relative risk was estimated by the Mantel-Haenszel approach but maximum likelihood (Marshall and Jackson, 1993) would have been an alternative. Maximum likelihood is especially appealing because it is quite general and can account for joint non-independent exposures (Marshall and Jackson, 1993).

In conclusion, the case-crossover design provides a means of answering the question: «What unusual thing was the animal doing prior to its illness or death». The utility of the approach compared with a traditional case-control design will depend on the relative susceptibilities of each method to selection and information biases and the ability to reconstruct histories of «usual» exposure patterns, a necessary prerequisite for construction of prior frequency distributions (Maclure, 1991; Marshall and Jackson, 1993). The relative efficiency of control sampling strategies in case-crossover designs warrants consideration and for this the reader is referred to Mittleman et al. (1995).

BIBLIOGRAPHY

Carrier TK, Estberg L, Stover SM, Gardner IA, Johnson BJ, Read DH, Ardans AA. 1997. Return from lay-up and risk of complete humeral or pelvic fracture in California Thoroughbred rachorses. J Am Vet Med Assoc (submitted).

Estberg L, Gardner IA, Stover SM, Johnson BJ, Case JT, Ardans A. 1995. Cumulative racing-speed exercise distance cluster as a risk factor for fatal musculoskeletal injury in Thoroughbred racehorses in California. Prev Vet Med 24, 253-263.

Estberg L, Stover SM, Gardner IA, Drake C, Johnson BJ, Ardans A. 1996. High speed exercise history and catastrophic racing fracture in Thoroughbreds. Am J Vet Res 5,1549-1555.

Estberg L, Gardner IA, Stover SM, Johnson BJ. 1997. A case-crossover study of intensive racing and training schedules and risk of catastrophic musculoskeletal injury and lay-up in California Thoroughbred racehorses. Prev Vet Med (submitted).

Jones BH, Harris JM, Vinh TN, Rubin C. 1989. Exercise-induced stress fractures and stress reactions in bones: epidemiology, etiology, and classification. In: Exercise and Sport Sci Reviews, Ed. Pandoff KB., 17, 379-422.

Maclure M. 1991. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 133, 144-153.

Marshall RJ, Jackson RT. 1993. Analysis of case-crossover designs. Stat Med 12, 2333-2341.

Mittleman MA, Maclure M, Robins JM. 1995. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. Am J Epidemiol 14, 91-98.

Roberts I, Marshall R, Lee-Joe T. 1995. The urban traffic environment and the risk of child pedestrian injury: a case-crossover approach. Epidemiol 6, 169-171.

Rothman KJ.1986. Stratified analysis. In: Modern Epidemiology. Boston: Little, Brown & Co, p196.