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Epidemiological evidence in forensic pharmacovigilance

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Abstract. Until recently epidemiological evidence was not regarded as helpful in determining cause and effect. It generated associations that then had to be explained in terms of bio-mechanisms and applied to individual patients. A series of legal cases surrounding possible birth defects triggered by doxylamine (Bendectin) and connective tissue disorders linked to breast implants made it clear that in some instances epidemiological evidence might have a more important role, but the pendulum swung too far so that epidemiological evidence has in recent decades been given an unwarranted primacy, partly perhaps because it suits the interests of certain stakeholders. Older and more recent epidemiological studies on doxylamine and other antihistamines are reviewed to bring out the ambiguities and pitfalls of an undue reliance on epidemiological studies.

Keywords: Epidemiological evidence, cohort studies, case control studies, statistical significance

1. Background

This paper addresses the role of epidemiological evidence in contributing to an assessment of cause and effect in forensic pharmacovigilance. It does so by outlining a case in which epidemiological evidence has been held to play a key role in determining causality but it applies this evidence to a new scenario and calls on the reader to make a judgment about how to balance inputs from epidemiological and other domains when it comes to issues of informed consent and by implication possible causality.

Standard methods of determining cause and effect based on Koch's postulates or the Bradford-Hill criteria were challenged in the 1970 s by legal cases linking a drug given for morning sickness, the antihistamine doxylamine (in Bendectin), to a range of birth defects. In the wake of thalidomide, evidence that doxylamine could be teratogenic in some animal species led to verdicts for plaintiffs born with birth defects following doxylamine intake in pregnancy – until a series of epidemiological studies cast doubt on the linkage [1].

The Bendectin case marked a point where epidemiology was given a central role in debates on the determination of causality in medico-legal settings. Up till then epidemiological studies had not been regarded as a good method to determine cause and effect, given that the associations they provide are perceived as particularly susceptible to bias due to confounding by indication or other factors. But when

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epidemiological studies subsequently also cast doubt on the risks of connective tissue disease from breast implants, their appeal grew – particularly for large corporate defendants, as they can be conveniently costly and time-consuming to mount.

The argument advanced was that epidemiological studies made it possible to offer estimates on the reliability of observations in a way that case studies and other approaches did not and they were therefore superior even to case studies in which challenge, dechallenge and rechallenge (CDR) were recorded [1, 2]. That anything other than epidemiological studies and controlled trials was junk science. In the following decades all case studies, even those involving CDR or dose responsiveness, have been degraded to the status of anecdotes [3].

2. Case-study

In cases of birth defects some method other than challenge, dechallenge, rechallenge and testing for dose response must be used to establish possible causation. But far from being conclusive, the case of doxylamine brings out the ambiguities of epidemiological studies almost better than any other body of evidence.

A series of three large cohort studies provided the basis for an argument against a linkage between doxylamine and birth defects [4–6]. Based on these data, the Courts had little option but to regard claims that the drug caused birth defects as possible "junk" science. It was this series of cases that gave rise to the famous Daubert v Merrell-Dow ruling that shapes almost all actions against pharmaceutical companies to this day, a ruling that put a premium on reliable evidence [2].

There have been a number of subsequent cohort and case-control studies [7–20]. Some of these have thrown up increased odds ratios or relative risks of birth defects on doxylamine [7, 9, 10, 12, 13, 16, 19], as did the earlier studies for specific defects such as pyloric stenosis [4, 6]. These make the picture more complicated despite the fact that some studies do not show the same problems [8, 11, 14, 15, 17, 18, 20]. The later studies have not attracted attention perhaps because for the most part the confidence intervals cross 1.0 and some will disregard the results accordingly as not statistically significant.

Since the early studies were done several sources of confounding in any study involving treatments for morning sickness have become clear. One is that women with nausea and vomiting in pregnancy may be at less risk of malformations than unaffected women [14]. A second hinges on a greater appreciation of the critical exposure periods for birth defects. Thus cardiac malformations are most likely following exposure to teratogens from weeks 3 to 8; given that women taking medication for morning sickness are unlikely to do so before week 6 and most likely to do so after week 8, this means that even a clear teratogen given for morning sickness would not be very likely to cause heart defects. Third, the early studies were done before ultrasounds and a range of other instruments became available to facilitate the detection of cardiac defects in particular.

More recently there has been concern about the potential of serotonin reuptake inhibiting antidepressants to cause birth defects [21]. A series of epidemiological studies have demonstrated an increased risk of major malformations and in particular cardiac defects on SSRIs (most clearly for paroxetine) [21]. These drugs also appear to increase rates of miscarriage. Paroxetine is now a Category D drug, meaning that it "causes" birth defects. The magnitude of the relative risks and odds ratios in the studies that have led to this labeling is very similar to the set of relative risks outlined in doxylamine studies undertaken in the 1980 s. The difference between the SSRI and doxylamine studies lies in the greater number and size of the studies, so that the confidence intervals in a number of the SSRI studies and in the studies

combined are quite tight. There is a *de facto* bureaucratic convention that forces regulators to act when confidence intervals for treatment hazards do not contain the figure 1.0.

The SSRI studies bear on the doxylamine story in that most of the SSRIs are antihistamines and a number of the antihistamines are serotonin reuptake inhibitors. A recent study from the Center for Disease Control has looked at the risk of birth defects on anti-histamines [22]. It concluded that antihistamines as a group are not linked to birth defects but noted a number of positive associations between diphenhydramine, doxylamine and chlorpheniramine and birth defects, not found with other antihistamines. A common feature of these three anti-histamines is that they act on the serotonin system whereas most of the others do not [23–25].

The tricyclic antidepressants are another group of drugs that help develop this issue. These drugs, which are not ordinarily thought of as serotonin reuptake inhibitors, have also been linked to birth defects and the more potent their effects at the serotonin reuptake site the more likely the risk of a birth defect [26]. These drugs are also antihistamines.

3. Appraising the evidence

Doxylamine continues to be used to treat morning sickness. It is also currently in a clinical trial as a prophylactic agent to be given to pregnant women to stop them developing morning sickness, with its manufacturer likely to seek a license should the trial prove successful [27]. For this purpose, "as soon as a patient becomes aware of the pregnancy, and before the Nausea and Vomiting of Pregnancy (NVP) starts, she will begin taking Diclectin" [28]. Women recruited to this study will therefore be systematically exposed to doxylamine earlier in pregnancy than would happen if just put on the drug following the development of morning sickness.

What should the informed consent forms for this trial tell women being recruited to the study? Should the information be shaped by a simple consideration of whether on balance the data from previous epidemiological studies are statistically significant or not, or that regulators have concluded that at present no risk has been demonstrated? Given that there is a systematic bias in doxylamine usage that makes epidemiological studies of this drug likely to miss the heart defects this drug may be at risk of causing, should the effects of this drug on the serotonin system and the effects of serotonergic drugs on the developing heart be taken into consideration?

John Snow is commonly credited with undertaking the first epidemiological study when he mapped the occurrence of cholera cases around Bow Street in London. Snow's maps are taken to illustrate possible causation even though the results are not framed in terms of statistical significance. Precisely because of the scope for confounding in Snow's study, for many people Koch's laboratory demonstrations two decades later of cholera bacilli taken from affected individuals carried more weight than Snow's epidemiology [2]. Koch's demonstration ultimately also carried more weight than the case study of von Pettenkoffer who drank a broth of cholera bacilli did not catch the disease and used this to claim that this bacillus did not cause cholera [2]. Von Pettenkoffer's challenge gave rise to Koch's postulates and ultimately the Bradford-Hill criteria.

The use of doxylamine as a prophylactic treatment for morning sickness offers us a modern take on the balance to be struck between epidemiology, case studies and laboratory demonstrations but one that at present we have to address without the benefit of hindsight. This case brings out the unreliability and potential invalidity of epidemiological evidence compared with case studies, but also the uncertain weight to put putative mechanisms of actions.

A further example may help illustrate the difficulties with epidemiological studies. It is in principle close to impossible to design a conclusive epidemiological study, whether case-control, cohort or clinical trial, to establish the suicide risk of antidepressants. Any relative risk or odds ratio that might stem from such a study hinges critically on the suicide risk of the population studied. A population with a low suicide risk may yield a diametrically opposite estimate to one with a higher risk [29]. The only way to get beyond a simple statement of "frequency in the study population" would be to have a test-retest component built into the clinical trial or cohort study.

This background should make it clear that forensic pharmacovigilance is a discipline that will need to avail of a range of methods. None can be held to be a gold standard that trumps others. Epidemiological evidence in this domain will always be provisional and rarely decisive.

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