Eur J Med Res (2004) 9: 545-551

An Internal Standard for Verifying the Accuracy of Serious Adverse Event Reporting: The Example of an Acupuncture Study of 190,924 Patients*

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Abstract
Background: Reporting of all serious adverse events (SAEs) is a requirement for regulatory approval of a drug. Can equally rigorous reporting standards be expected in studies of non-drug treatments and how can underreporting, if any, be detected and proven? Using data from our large-scale prospective cohort study of acupuncture on outpatients, we examine the use of an internal standard, a principle taken from laboratory medicine, to quantify real event rates.
Methods: A total of 190,924 patients (68.6% women) seeking treatment for chronic pain (headache, low back pain, coxarthrosis or gonarthrosis) from 12,000 physicians in private practice in Germany were observed during a six-month period ending in May 2002. Most received ten sessions of body acupuncture. Mean treatment time was six weeks. All practitioners were certified in acupuncture and received written instructions on completing forms for basic patient data and SAE monitoring. They were also informed that payment by insurers would be made only upon return of the completed form. All SAEs occurring between start of the first acupuncture session and end of the last one were to be reported, whether causally related to the treatment or not. Multiple minor adverse events (AEs) per single patient were to be reported only once. As the internal standard we chose the expected number of deaths, based on the death rate for the German population, adjusted for age, sex distribution and mean observation time of our study patients.
Results: 45 SAEs and 14,404 AEs were reported (i.e. 2.4 SAEs and 754 AEs per 10,000 patients). The number of reported deaths (9) was only 5% of the statistically expected number (180). Applying the resulting correction factor of 20 to all reported SAEs, resulted in 900 expected SAEs (versus 45 reported) or 47 per 10,000 patients.
Conclusions: Without verifying the accuracy of a measurement, results remain speculative. Our internal standard for the first time provides a means of verifying the accuracy of the reported SAE rate and correcting it to the statistically expected SAE rate.

Key words: Body acupuncture; prospective cohort study; adverse events; internal standard; underreporting

List of abbreviations used: AE = Adverse Event; SAE = Serious Adverse Event

Introduction

A consensus exists on the importance of adverse patient outcomes in the health care system. There is no consensus, however, on numbers that have been reported in the recent past [12, 16]. This is hardly surprising, since so far we have no way of knowing whether reported event rates are accurate, especially among outpatients. Two recent studies, both carefully conducted, found that adverse events among outpatients are common [9, 10]. A comparison of the data from the two studies, however, reveals quite different adverse event rates.

This discrepancy reflects one of the basic problems of any measurement method. How do we know that what we have measured is accurate? How can we know the real frequency with which adverse events, for example, occur? In a thoughtful paper, Thomas et al. [23] looked at eight measurement methods that are normally used in health care, and found that not one of the eight methods could claim to determine all event rates reliably and accurately. For example, trained chart reviewers may have poor inter-rater reliability [22]. Medical personnel interviewed directly may be under time pressure, or concern for one's reputation may influence whether adverse events are reported or not [13, 23, 25]. When patients are interviewed, communication problems between caregivers and patients on the one hand [9] and the problem of patient recall bias on the other hand must be taken into consideration [7, 14]. The underlying problem remains: how can researchers determine whether the reported SAE rate corresponds to the actual number of events, if they have no idea how frequently these events should be expected to occur? The question of how to be sure that the values we are measuring correspond to real values is not new, and the field of laboratory medicine offers a possible answer.

*Part of this article was presented as a poster at the 10th Annual Symposium of the Society of Acupuncture Research, November 15th – 16th, 2003, Harvard School of Education, Cambridge, MA

It has long been an accepted principle of all analytical methods that it is not sufficient to measure a value without at the same time verifying whether the measurements are accurate. The lack of knowledge about the true size of a measured value is solved by the addition of an internal standard, which is as similar as possible to the substance under investigation. When performing quantitative determinations by means of HPLC or GC chromatography, for example, the comparison between the peak of the internal standard (of known quantity) and the peak of the test substance (of unknown quantity) can be used to calculate the real concentration of the test substance regardless of possible losses in the measuring apparatus, since the molecular similarity between the test substance and the internal standard guarantees that all losses or measuring fluctuations affect both substances the same way. It seems reasonable that this basic idea could be applied to the problem of determining and correcting for "measuring losses" (i.e. underreporting) associated with SAE rates. To our knowledge our acupuncture study is the first time this idea has been applied.

The ICH definition of an adverse event (AEs) is any untoward medical occurrence experienced by patients, temporally but not necessarily causally associated with the use of a drug or medical treatment, [2, 5], and a serious adverse event (SAEs) is defined, according to the ICH, as an adverse event that results in a life-threatening condition or death, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity, including congenital anomaly/birth defects. Because our target parameter was the number of SAEs reported, the internal standard would have to be an SAE as well, and one for which the actual number of cases is known with a high degree of accuracy. We therefore decided to use the official death rate (taken from German population statistics) as an internal standard, because it is precisely known and because the death of a patient is information of which no physician is likely to be unaware. This known death rate was then compared with the reported death rate in our study leading to a correction factor for the number of SAEs reported.

METHODS

The GERAC (German Acupuncture) cohort study, launched in March 2001, involved 12,000 physicians in private practice throughout Germany. 52.4% were general practitioners, 19% orthopedists, 9.4% internists, 3.9% gynecologists, 3.8% anesthetists, and 11.5% a variety of other specialties. All physicians held a certificate in traditional Chinese acupuncture, requiring at least 140 hours of formal acupuncture training, and all had signed a study contract. We estimate that these physicians provide acupuncture to well over 600,000 chronic pain patients a year. The nearly 200,000 patients in our sample sought acupuncture treatment for chronic pain (headache, low back pain, coxarthrosis or gonarthrosis) from November 2001 through May 2002. They were of all ages and all were insured by the insurance providers funding our study. Patients (or their parents) were informed about the study by their physicians, signed an informed consent if they wished to participate, and underwent an examination to determine eligibility (for inclusion and exclusion criteria see Table 1).

Those eligible normally received a series of ten acupuncture sessions, two per week. After the last session, physicians were required to report basic patient data and adverse events, if any, on a standard form to our data centre (fax being the preferred method). AEs that occurred more than once per patient, for example haemorrhage, were to be reported only once. No follow-up was conducted. In a covering letter, the physicians were instructed on how to complete and return the forms. It was also pointed out that payment by the insurer would be made only upon return of the completed form. The forms contained a short list of known minor adverse events (in particular vasovagal reactions and aggravation of symptoms [15, 27]). Each type of event was counted only once per patient, regardless of how often it occurred. This was done intentionally. Multiple occurrences of haematoma, for example, tend to reflect patient-specific characteristics such as a mild coagulopathy and, if reported each time, would lead to a falsified picture of acupuncture AEs. There was no attempt to categorize reported SAEs by severity as serious, life-threatening, or fatal. In all cases

Table 1. Inclusion and exclusion criteria in general.

Indication	Inclusion criteria	Exclusion criteria
Headache	Migraine or tension-type headaches, presenting for more than 6 months, patient publicly insured, able to speak and read German, written informed consent	Headaches caused by specific pathological entities such as meningitis, meningeal bleedings, expanding processes, febrile illness, illness of the nasal sinuses, glaucoma, arterial hypertension or other extracranial or intracranial process of organic cause (so-called secondary headaches)
cLBP	Chronic lower back pain presenting for more than 6 months, patient publicly insured, able to speak and read German, written informed consent	Back pain due to e.g. malignant processes, compression fractures, spondylitis ankylosans, Reiter's syndrome, Paget's disease, etc., spondylolisthesis, infectious spondylitis, pyelonephritis
Arthrosis	Coxarthrosis or gonarthrosis, presenting for more than 6 months, patient publicly insured, able to speak and read German, written informed consent	Arthrosis pain due to e.g. malignant processes, infectious coxarthritis or gonarthritis, rheumatoid coxarthritis or gonarthritis

in which an SAE was reported, the reporting physician was called and asked to provide details of the case.

The study protocol was approved by local ethics committees. Only patients who gave written informed consent were considered. The study was conducted in accordance with the Declaration of Helsinki and GCP guidelines.

RESULTS

205,808 patient data forms were received on our fax server in the first half-year of 2002. After elimination of duplicate or illegible forms (nearly 15,000), a total of 190,924 patients remained. The patient data are shown in Table 2.

Patient ages ranged from 2 to 97 (Fig. 1). Only 15.9% were below the age of 40. Thirty-one patients were between 2 and 5 years old (two 2-year-olds, two 3-year-olds, nine 4-year-olds, and eighteen 5-year-olds), all being treated for cephalalgia. Sixteen patients were between 95 and 97 years old (ten 95-year-olds, five 96year-olds and one 97-year-old), of whom seven were being treated for arthrosis, seven for low back pain, and two for cephalalgia.

82.4% of all patients received ten acupuncture sessions, 15.7% underwent fewer than ten sessions for unspecified reasons, including relief from the condition for which treatment was sought, and 1.9% of all patients underwent more than ten sessions (usually 15). The total number of sessions exceeded 1.77 million. In the majority of cases (56.2%), ten acupuncture sessions were given over a period of four to eight weeks (two sessions per week), in 26.8% of cases over a period of more than eight weeks, and in the remaining 17% over a period of less than four weeks. The mean observation time for patients with exactly 10 sessions was 46.5 ± 26.5 days, and the mean observation time for all patients (including those who had less than 10 acupuncture sessions) was 44.9 ± 27.6 days.

All patients were classified according to sex and age (five-year blocks). The age blocks matched those used in the official death tables in the Statistical Yearbook of the Federal Republic of Germany. [3] Multiplying the death rates per age block in those tables by the number of patients per sex and age block in our study and adjusting for the mean observation time, one finds that a total of 180 deaths would be statistically expect-

Table 2. Patient data and chronic pain indications for 190,924 patients (physician checks off the appropriate box).

				Acupuncture Indication (% of all patients)			
Patients	**Percent**	**Mean age (± SD)**	**Median age**	**Arthrosis**	**Chronic low back pain**	**Headache**	**More than one or wrong indication**
Female	68.6%	57.5 (15.6)	60	7.0%	33.7%	16.2%	11.7%
Male	31.4%	54.9 (15.0)	57	2.8%	18.8%	5.3%	4.5%

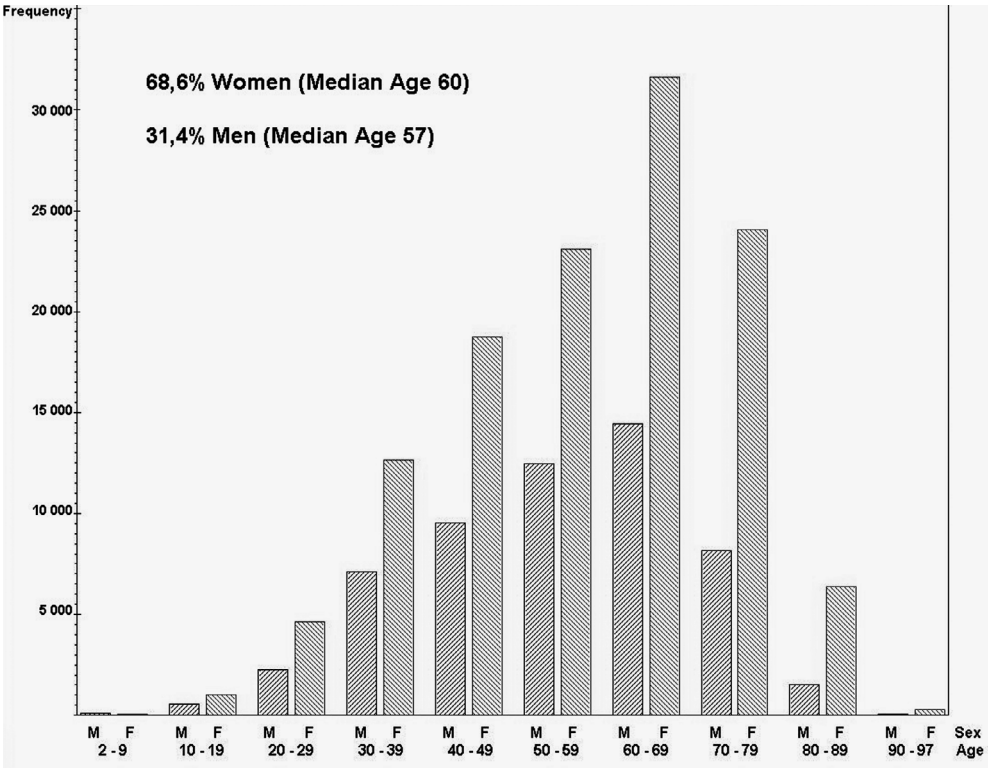

Fig. 1. Age and Sex Distribution of all 190,924 Acupuncture Patients.

Table 3. Brief description of serious adverse events reported in 190,924 patients receiving acupuncture treatment.

SAE (from telephone interviews with the physicians)	**Number of patients reported**
Death	9
Fall or trauma, with or without fracture (1 caused by an antihypertensive treatment, 1 caused after acute obstructive respiratory distress syndrome in a heavy smoker, 1 distortion of left knee by trauma, 1 unknown reason)	4
Acute general infection with hospitalisation (1 Lyme disease, 1 unknown)	2
Allergic reaction to concomitant medication (atopy)	1
Stroke with hospitalisation (1 cerebral thrombosis, no details given for others)	3
Intervertebral disk prolapse (surgical treatment), pain exacerbation (hospital admission)	5
Cardiovascular problems (hospital admission)	3
Malignant parotis tumour (hospital admission)	1
Hospitalisation (unknown reasons)	17
Number of patients with SAEs (all reports)	45

Table 4. Descriptions of the 9 deaths reported among 190,924 patients receiving acupuncture treatment.

Description of reported deaths (from telephone interviews with the physicians)	**Number reported**
Long-standing cardiac illness suspected as cause of death (male and female patients between 71 and 87 years of age)	4
Carcinoma as cause of death (67-year-old patient with oropharyngal carcinoma and 81-year patient with bile duct carcinoma)	2
84-year-old patient suffering from atherosclerosis for many years, particularly also an atheromatosis of the aortic arch; cause of death: stroke	1
Death from pneumonia in 82-year-old patient who had suffered from pulmonary emphysema for many years	1
86-year-old patient, in treatment for many years for hypertension, hyperthyroidism and gout, struck by car while crossing the street on her way home from the sixth acupuncture session, subsequently died in hospital of her injuries. The accident occurred near the patient's home, not outside the physician's practice.	1
Total	9

Table 5. Minor adverse events or side effects reported in 190,924 patients receiving acupuncture treatment.

Event	**Number of patients reported**
Administration and application site problems:	
Broken needle	1
Blister following moxibustion	1
Local skin infection	86
Local allergic reaction (urticaria)	19
Severe pain at site of needling (local or radiating)	90
Haematoma	9,896
Vasovagal reactions:	
Collapse, dizziness, nausea, vomiting	1,342
General problems:	
Drowsiness, sleep disturbances (especially at beginning of treatment phase)	72
Aggravation (temporarily) of existing ailments	2,494
Neurological and psychological problems:	
Needle phobia, anxiety and rage	49
Depressed emotional state, neurovegetative dystonia	23
Emotional release (feeling relaxed, general emotional well-being), euphoria	49
Tingling, prickling, burning dysaesthesias, paraesthesia, hyperaesthesia during acupuncture treatment (not in the meaning of De Qi sensations)	157
Others:	
Concomitant diseases of recent appearance (temporary or permanent)	70
Miscellaneous symptoms, not described in detail	55
Number of patients with at least one of the above minor AEs or side effects (of these, 357 experienced more than one type of AE)	**14,404**

ed to occur during this time among 190,924 patients (internal standard).

A total of 45 SAEs were reported (Table 3), including nine deaths (Table 4). This represents an underlying reported SAE incidence of 2.4 per 10,000 patients.

The reported death rate (9 per 190,924) is only 5% of the expected death rate (internal standard = 180 per 190,924). Applying the resulting correction factor of 20 to all reported SAEs yields an expected SAE rate of 900 (20 x 45) among 190,924 patients during the mean observation time, or 47 SAEs per 10,000 patients (with the age and sex distribution of our sample).

Telephone interviews with all 45 physicians who reported SAEs revealed that in all cases, the physician had reported the event only to give a reason why the acupuncture treatment was terminated earlier than planned. The interviews also revealed that in 17 of the 45 SAE cases (38%) the physicians had only a very vague idea of what had happened to their acupuncture patients since the termination of treatment. They knew that their patients were hospitalized, but knew nothing about the reasons for hospitalization.

In addition, 14,404 minor adverse events were reported (754 per 10,000 patients), the most common being haematoma (518 per 10,000 patients), aggravation of existing ailments (131 per 10,000 patients), and vasovagal reactions (70 per 10,000 patients) (Table 5). Each type of AE was counted only once per patient. More than one type of minor adverse event was reported in only 357 patients (four AEs in 24 cases). The most frequent combinations reported were haematoma and vasovagal episode (146 cases) and haematoma and aggravation of existing symptoms (139 cases).

Minor adverse events could not be corrected for underreporting because the internal standard (number of deaths) is not similar enough to mild or moderate AEs. Localized erythema at application site (46,682 patients i.e. almost 25% of all patients), often regarded as desired acupuncture reaction, were not taken in account for the minor adverse events.

Discussion

In the absence of a method of verifying the reliability and validity of reported data, it is not surprising that the actual extent of SAEs remains the subject of considerable debate [12, 16] How widely these numbers can differ is shown by recent publications on serious adverse drug reactions in outpatients, [9, 10] as well as on adverse event rates in hospitalized patients. [21, 24, 26] Even where identical measuring methods are used, there is no guarantee that the data will be comparable. [26]

Because of the importance of reliable reporting of SAEs [9, 10, 13, 19], regular monitoring of participating physicians is carried out in industry-funded studies to ensure a picture of potential harms as complete as possible. This procedure corresponds to GCP and is required by the regulatory authorities. [19] However, in studies that are not aimed at obtaining regulatory approval for pharmaceutical products, such monitoring visits are rarely carried out because of their high cost, and consequently adverse events are reported significantly less often. [4] This illustrates the need for an internal verification mechanism for the reported number of SAEs, e.g. the internal standard in our study. As in laboratory medicine, the internal standard must be as similar as possible to the parameter under investigation.

Many reasons have been given to explain why reported adverse event rates may not be accurate. [1, 8, 9, 22, 23] Internal standards are particularly necessary to enable verification of measured adverse event rates in outpatient study populations. Because no such standard has been used in the past, claims that acupuncture is a method resulting in few if any SAEs [6, 11, 15, 17, 20] remain open to question. In the absence of a more rigorous method, some authors have tried to estimate a maximum limit for the incidence of SAEs in conjunction with acupuncture treatment. [15, 27] However, when our internal standard is applied to previously published SAE data, underreporting is quickly identified. For example, in two recently published acupuncture studies [15, 27, 28] covering a total of 66,229 acupuncture treatments (or 13,245 patients if one assumes, as the authors do, an average of five treatments per patient), not a single death was reported, nor were any other SAEs.

It is important to bear in mind that no one can know how many SAEs that are causally linked to the treatment under study actually occurred, as long as rates of reported SAEs diverge widely from the SAE rates to be expected after internal standard correction. Unless all SAEs during the study period are reported, it is impossible to determine how many of them are causally related to the treatment being studied, because while unreported SAEs may have been purely coincidental, they may also have been causally linked to the treatment. SAEs that are causally related to a particular treatment need not, of course, occur simultaneously with the actual treatment session, but may take place hours or even days later. Once the patient has left the doctor's office, it does not mean that a subsequent SAE has nothing to do with the treatment. Thus the death of a patient in our study who was hit by a car while crossing the street after her acupuncture session cannot be interpreted a priori as being completely independent of the treatment.

Incorrect SAE data do not occur only in conjunction with studies in complementary medicine. They are a fundamental problem in medical research. One of the reasons for this, based on the results of our telephone interviews, is a general reporting bias among physicians who are unaware of the importance of reporting SAEs. The 45 physicians we interviewed found the idea of reporting events that "are not necessarily causally related to the treatment" [2, 5] to be somewhat peculiar, and it seems safe to assume that the 'average physician' in Germany and elsewhere would react similarly, as illustrated by a recent publication [18] in which the authors conclude that "under identification" of AEs was mostly due to medical staff inadequately grasping the concept of adverse event. Other authors have pointed out that adverse reactions are more likely to be reported if they are unique, [11] and that low individual reporting rates may be due to a high personal threshold for reporting or misguided be-

lief about the irrelevance of a single SAE. [8, 27, 28] Aggravating this unsatisfactory situation, especially in outpatient populations, may be poor communication between different specialists caring for a patient. The lack of awareness in our cohort study of the causes leading to a patient's hospitalization is a realistic reflection of the situation of outpatient care.

Another problem not to be overlooked is publication pressure. Uncertainty about the real frequency of adverse events can be due in part to a general aversion to describing over- or under-reporting. This is not surprising. Editorial boards tend to reject for publication studies in which the authors themselves give evidence of over- or underreporting. Peer reviewers tend to interpret acknowledgement of the problem as a sign of methodological inadequacy, rather than seeing it for what it is, namely a sign of methodological quality, because the authors make visible a factor that would otherwise remain invisible.

Conclusions

There are several conclusions to be drawn. First, all physicians participating in a clinical trial need to be carefully trained to identify and report all adverse events. It must be made clear that SAEs include all events that occur during the specified period, whether causally related to the treatment or not. Second, participating physicians need to be explicitly instructed to determine the cause of every single SAE, even when this involves additional time and effort. Simply reporting that a patient has been admitted to hospital, without knowing the reason for hospitalization, is not enough. We conclude, thirdly, that a suitable internal standard should always be recorded along with the rest of the data. These efforts would be highly worthwhile in that they would enable us to more reliably assess the harms and risks of new or established treatments.

Funding:
The GERAC trials are funded by the following German public health insurance providers: AOK, BKK, IKK, Bundesknappschaft, Bundesverband der Landwirtschaftlichen Krankenkassen, and Seekasse.

The funding organizations played no role in the design or implementation of the study, in the collection, management, analysis or interpretation of the data, or in preparation and review of the manuscript.

On behalf of the steering committee of German Acupuncture Trials (GERAC):
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Received: October 14, 2004 / Accepted: November 22, 2004

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