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Abstract
Influential American medical organizations and publications have published guidelines for the treatment of acute migraine headaches that omit antiemetics, usually suggesting triptans as the first line of treatment. A review of the few comparative studies directly contrasting clinical outcomes of triptans and antiemetics in the treatment of acute migraines suggest that both treatment options are relatively equal in efficaciousness. The added burden of triptan usage, including an added risk of adverse effects and a high cost per dose, would seem to warrant an antiemetic-first approach to migraine treatment, as recommended by several international health communities. Possible reasons for the prominent omission of antiemetics from leading publications may include medical parochialism and pharmaceutical funding of medical research.

Introduction

In January 2002, the New England Journal of Medicine published a paper entitled "Migraine-Current Understanding and Treatment," written by several leading neurologists. The paper reviewed all the current treatment options for migraine headaches, and strongly emphasized triptans, a relatively new class of drugs developed by drug companies specifically to address migraines (Goadsby et. al., 2002). One of the most notable aspects of the paper was that it completely omitted the drug class antiemetics, which is increasingly used nationally and internationally, mostly among emergency medicine practitioners, to treat acute migraine headaches (Seguil & Lax, 2014). One factor for this omission may have been the varied perspectives which can often develop between members of different specialties of medicine, with neurologists recommending one therapy and emergency medicine doctors recommending another (Newman, 2009). Nevertheless, it is likely that the authors were aware of the therapeutic history of antiemetics for migraine headaches, and they chose to omit it. In fact, the papers recommendations are completely consistent with the guidelines published by the American Academy of Neurology (n.d.). The purpose of this review is to assess whether these influential omissions are in fact warranted by clinical observation and meta-analysis, or if antiemetics should be considered an efficacious treatment for acute migraines with the right clinical indications. Possible biases that could have caused conscious or subconscious influences on the recommendations of different groups will also be analyzed as a method of understandings them.

Methods

In order to assess antiemetics as an efficacious treatment option for acute migraines, a meta-analysis of the published literature was undertaken. Comparative studies between the effectiveness of triptans and antiemetics is the main focus. In assessing clinical value, both primary effectiveness and secondary side-effect prevalence were surveyed to accurately portray an overall picture of patient outcomes. Clinical trials were obtained using the National Institute of Health's PubMed search engine, and only studies published in reputable academic journals were included.

Migraine Headaches

A migraine headache is defined as a headache that usually affects one specific area or side of the head and is frequently accompanied by nausea, sensory sensitivity, and possible neuralgia (Ferrari, 2013). Headaches accompanied by neuralgia have been recorded since ancient times, as far back as the ancient Egyptians (Miller, et. al. 2005). The difference between a normal headache and a migraine is often one of degree and thus cannot always be definitively assessed; however, chronicity can be an important indicator of migraines. The first modern treatment for migraines was ergotamine (Woakes, 1868), which was originally hypothesized to slow the stimulation of sympathetic nervous pathways (although its mechanism is now contested). The pathogenesis of migraines was illuminated in the 1940s, when serotonin was isolated as a potent cause of migraines (Wolff, 1948). This discovery led to the serotonin-inhibiting class of migraine treatments, starting with methylsergide, which was first used in the middle of the 20th century (Sicuteri, 1959).

This paper focuses on two modern therapies for migraine headaches: triptans, of which the prototype drug is sumatriptan, discovered in 1988, and antiemetics, which are primarily anti-nausea medications, including domperidone, metoclopramide, and prochlorperazine. These drugs are typically given together with an analgesic, usually aspirin. Other commonly used pain-relieving drugs, such as NSAIDs, caffeine, and codeine should be noted, but are not of specific interest to this discussion.

Triptans

Triptans were first used in the treatment of migraines during the 1980's, when interest surged in examining the role of serotonin (5-HT) in the pathogenesis and pathophysiology of migraines (Bateman, 2000). Triptans are a class of drugs that affect serotonin receptors, commonly called 5-HT receptors, of which there are many subtypes. Triptans are 5-HT agonists, binding with high affinity to many 5-HT subtypes that cause potent vasoconstriction of many intracranial blood vessels. They also affect various neurotransmitters and chemical mediators, but no specific effect has been conclusively tied to theiranti-neuralgic properties. Because of a variety of concerns regarding the effectiveness of the original triptans, such as variable bioavailability, variable absorption, and significant adverse effects, new classes of triptans have been continuously developed by drug companies. Some of

the most recent triptans typically prescribed for migraine headaches include almotriptan, frovatriptan, and avitriptan (Loder, 2010). Although the mechanism of the therapy remains unclear, it is generally recognized in the United States as a first-line therapy for patients unresponsive to analgesics. Triptans provide relief of symptoms within the first 10-60 minutes of use, depending on route of entry (Loder).

Antiemetics

Antiemetics are drugs that relieve symptoms of vomiting and nausea. They are usually used to treat motion sickness and to relieve the side effects of nausea-causing therapies. The use of antiemetics as a direct therapy for migraine headaches was a serendipitous discovery. Originally, antiemetics were used to allow sufferers of migraines to ingest drugs given to relieve the headaches. However, physicians soon began to notice that the symptoms of the migraine headaches were relieved before the primary therapy could be given. Thus antiemetics soon became the drug of choice, especially among emergency medicine practitioners, to treat analgesic-resistant headaches (Newman, 2009).

Comparative Studies

Unfortunately, and for possible reasons that will be addressed further, there are very few studies that directly compare the efficaciousness of triptans and antiemetics in the treatment of migraine headaches (Gupta et. al., 2002). However, a number of studies have been completed globally that directly contrast these two treatment options.

The first comparative study was published in 1995, comparing oral sumatriptan (a triptan) with lysine acetylsalicylate plus metopramide (an aspirin plus an antiemetic) in their effectiveness in treating migraines (Tfelt-Hanson et. al., 1995). This study was conducted between October 26, 1993 and July 18, 1994 at over 68 medical centers in Belgium, Denmark, the Netherlands, and France, and included only patients with significant histories of migraine headaches. It was a randomized, double-blind study, which included follow-up for up to as eight weeks, as needed. Four hundred twenty-one patients participated in the study. The study showed that in numerous benchmarks for effectiveness, the two treatment options were virtually identical, including improvement in immediate headache severity, control of adverse effects, headache recurrence, and patient satisfaction. The authors concluded that "there is no difference in primary or secondary efficacy between LAS+MTC and oral sumatriptan…because of its high price physicians should consider whether the routine use of sumatriptan as the initial treatment of a migraine attack really is preferable to the use of cheaper drugs such as analgesics combined with an antiemetic." Indeed, in Europe and in many other countries, these recommendations are generally considered best practice (Newman, 2009).

A subsequent study was performed in three medical centers in France, with a total of 666 participating patients (Geraud et. al., 2002). It was a multicenter, double-blind, randomized study, and follow up was performed until fifteen days after the last migraine attack took place. Each patient was given one of the following: acetylsalicylic acid plus metoclopramide, zolmitriptan, or a placebo. The patients were then requested to keep an hourly diary to record headache relief, overall pain relief, nausea levels, any adverse effects, and overall satisfaction with the therapy. The study results seemed to be inconclusive initially, as the authors wrote: "Both treatments reduced migraine-associated nausea, vomiting, phonophobia and photophobia. There were no important inter-group differences with respect to the onset of meaningful migraine relief, the frequency of headache recurrence, the usage or efficacy of a second dose of medication or the use of escape medicine." However, the authors preceded to perform what they called a "post hoc analysis," in which they found certain benefits to triptan use, including a greater overall patient satisfaction, overall pain-free reporting (as opposed to headache pain), a greater efficacy in patients with "migraine associated with menses," and the fact that triptan use was "unaffected by age, weight, or gender." They thus concluded that "Although evaluation using the primary end point in this study was inconclusive, other end points such as freedom from pain, now identified as more clinically relevant end points, showed zolmitriptan 2.5 mg to be significantly better that the standard analgesic-anti-emetic combination of acetylsalicylic acid and metoclopramide." In summary, this study found slight benefits to triptan use, although it is important to note that for all the primary end points designated before the study was completed, the therapies were identical. Only after the data was collected did the authors find certain benchmarks that could be identified as benefits to triptan use. This is generally considered a far less objective method of gathering data, as it allows the investigator considerable latitude in actively picking specific data sets. In what may be an important note, the study concludes with an acknowledgement that "this study was supported by AstraZeneca Pharmaceuticals."

A third study, performed in New York City, compared aggressive metoclopramide treatment, consisting of four infusions within the first two hours, to subcutaneous sumatriptan treatment of migraine headaches (Friedman et. al., 2005). Two hundred two patients participated in the trial. Patients were not followed after the initial twenty-four-hour period, which can be considered a weakness in their overall assessment of the therapies; in fact, only 37 of the patients completed the twenty four-hour follow-up protocol. In addition, the patient population studied was almost completely comprised of individuals of Latino origin, making extrapolations to general populations uncertain. Another concern is that the study excluded those suffering chronic migraines, which may be a population which reacts differently to specific therapies.

The study concluded that there were no significant differences between the two therapy options in reaching the primary end points of the study, including headache relief, nausea relief, and overall well-being. However, in their own post hoc analysis, the authors find certain benefits to metoclopramide use, including twenty-four-hour symptom relief.

A fourth comparative evaluation was performed in Iran at the Isfahan University of Medical Sciences, comparing metoclopramide to sumatriptan for migraine headache treatment (Talabi et. al., 2013). This study was performed on emergency room patients. One hundred twenty-one subjects were included in this randomized, double-blind study. Several introductory notes should be mentioned about this study. First, the command of the English language displayed by the authors is competent overall but nevertheless displays signs of possible grammatical and idiomatic peculiarities which may or may not result in important, altered connotations (for example, the authors wrote that their study included a "controlled study design and patient blindness"). Second, the study noted that "it is surprising that no subjects in both groups complained of adverse effects." This is a significant deviation from other comparable studies, which may be a cause for concern. The authors attempt to explain this discrepancy as "a result of slow metoclopramide injection and the way the question about these effects were phrased." It also may be a reflection of cultural differences in the way side effects are described, or how often, or upon what level of acuteness, they are remarked upon. The patients were all observed during the initial hour after they were treated. The results of this trial were that metoclopramide was superior to sumatriptan in headache relief (Talabi).

In summary, there are very few studies that directly compare triptans to antiemetics for acute migraine headache relief. The few that have been performed suggest that the therapies are relatively similar in effectivity for all primary end points.

Triptans vs Antiemetics: Other Differences

The fact that triptans and antiemetics have been shown to have similar outcomes in treating migraines does not necessarily mean that they are equally sound treatment options. In fact, there are several reasons why triptans may be a less advisable treatment option. The first is adverse effects. Triptans are known to cause several negative effects in patients. The most common set of adverse side effects, affecting almost half of all triptan users, is often referred to as triptan sensations, and includes upper chest pressure or pain and epithelial flushing. Rare cardiovascular events have also been reported and triptans are thus contraindicated in those with possible cardiac disease. This stands in contrast to antiemetics, and specifically to metoclopramide, which have minimal reported adverse effects. The second shortcoming of triptans is their often high price, with the average cost of a single triptan pill typically exceeding ten dollars, while a single dose of antiemetics can cost less than ten cents (Adelman et. al., 2004). The benefits of antiemetics are thus both in terms of adverse effects, which are minimal, and cost, as they are extremely cheap therapy to provide to patients. Therefore, if antiemetics can be shown to be comparably effective to triptans in specific clinical settings, which seems to be the case, they can plausibly be considered a superior therapy overall under those conditions. Thus it remains puzzling how the 2002 review article in the New England Journal of Medicine completely omitted antiemetics in its review of migraine relief protocols, and why it is omitted from the recommendations of the American Academy of Neurology on the treatment of migraines.

Medical Parochialism

Parochialism in research has been a phenomenon long noted and lamented by meta-researchers (March, 2005). It is often based on nationality, with different countries' research communities favoring different approaches. These differences can have cultural, ideological, or experiential origins. Parochialism can also be of disciplinary origin. In the medical field, this has often been the case; for example, medical doctors and nurse practitioners often find themselves at odds over a variety of disciplinary differences (Phillips et. al., 2002). In the specific case of the triptan vs. antiemetic debate, the difference in recommendations may have arisen from the different perspectives that neurologists and emergency medicine doctors have of migraine sufferers. Emergency medicine practitioners generally see patients who are in the midst of acute migraine attacks. Therefore, their perspective is geared toward therapies that are most efficacious at immediate migraine relief, and this may factor into their preference of antiemetics to triptans (Friedman et. al., 2014). Neurologists, on the other hand, see mostly patients who are chronic migraine sufferers, and may therefore strongly favor treatments that provide longer-lasting relief. Nevertheless, it must be emphasized that the review in the New England Journal of Medicine was a complete review of both acute and chronic migraine treatments, and thus explicitly included the medical protocols in which emergency medicine practitioners are most experienced. It is therefore quite possible that parochialism is at fault for the varying guidelines proposed to treat migraines, where one field's inherent biases led it to ignore or be unfamiliar with the practices of other fields. (It should be noted, however, that the 2005 study that found that antiemetics were comparable to triptans was authored by emergency room doctors and was published in the journal Neurology.)

Pharmaceutical Funding

Surveying the comparative studies of triptans and antiemetics brings to the fore the often uncomfortable question of relationships between for-profit companies and medical institutions and research facilities (Smith, 2003). Although many regulations have

been passed over the last few decades, which have helped prevent the more egregious practices of pharmaceutical companies, many interactions remain that might possibly compromise clinical objectivity (Brody, 2005). It is certain that drug companies would favor the use of expensive, patented triptans over the cheap antiemetic drugs, and it is thus distressing that a drug company was the primary funder of the single comparative study that found, in post hoc data examination, that triptans were a superior treatment option. The other studies were free of any reportable conflict of interest, and came to different conclusions. In addition, the review article from the New England Journal of Medicine, which strongly focused on and recommended triptan use, closes with a fine-print disclosure that all the authors have been recipients of grant funding or have acted as consultants for many different drug companies, including all those that currently manufacture triptan medications (Newman, 2009). This fact may explain why the authors, consciously or not, were especially focused on triptan therapy. Of course, this does not mean to slander the authors in any way or to impugn their professional reputation, but rather to bring into focus the problems associated with industry funding of scientific enterprises. Certainly, the fact that such funding is indispensable to many research projects cannot be ignored, but perhaps other remedies, such as the mandatory authorship of one author without reportable conflicts of interest, can be advanced to protect the integrity of these studies.

Another important question regarding pharmaceutical company funding of medical research is the types of studies performed. For example, if a pharmaceutical company deems a therapy to be dangerous toward its bottom line, it may simply withdraw all funding for studies pursuing that therapy, leaving little incentive for researchers to pursue it. This may explain why so few studies have actually been performed comparing triptans directly with almost any other therapy, including antiemetics, and instead most research in the field consists of large studies, including thousands of patients (Ferrari et. al., 2002), which look solely at the benefits of triptans.

Conclusion

A survey of comparative studies available shows that antiemetics are as suitable for treating acute migraines as triptans. The omission of this documented treatment from prominent guidelines and publications is disconcerting, and may point to several fundamental weaknesses in the current research and application model. Medical parochialism and pharmaceutical funding likely amplified these flaws, and must be addressed as part of the solution going forward.

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