Photo: Fotolia/Rob Byron

Scientist versus pharma company

Starch Nonsense

The debate about the use of starch solutions to maintain blood volume in intensive care is becoming more intense. Instead of helping to solve the debate, a drugs company is now threatening to sue the scientist who performed a critical clinical trial.

"I was shocked," remembers Anders Perner with a surprisingly calm voice. On Monday, 9 July the professor in intensive care medicine at the Rigshospitalet in Copenhagen received an email from lawyers representing the German pharmaceutical company, Fresenius Kabi, demanding that the physician correct certain details in his most recent article about a clinical trial. If he didn't agree to do so, the company would sue him and his PhD student. Fresenius Kabi obviously saw their business was under threat.

The conflict ignited over a clinical trial on the treatment of very low blood pressure as a consequence of severe inflammation of the whole body (severe sepsis/septic shock). Severe sepsis is a condition that affects about 0.3 percent of the population per year and lands them in intensive care departments. Between 40 and 60 percent of the patients die due to the resulting failure of the kidneys, lungs or other organs. When trying to save their lives with antibiotics, the blood pressure is commonly restored by replacing intravenous fluid.

Modified starch or simple salt?

Among physicians there is a decades-old debate about the kind of fluid that should be administered. Traditionally, this was just an isotonic salt solution (crystalloid). Unfortunately, the salt solution diffuses through the dilated blood vessels into the surrounding tissue. For about 50 years now, an alternative has been available: adding large molecules like modified starch to the liquid (colloid). These molecules do not leak through the endothelium so easily and, therefore, keep the osmotic pressure in the blood high. However, there has always been controversy about the benefits of this treatment on the one hand and possible serious side effects on the other hand, which could even kill patients.

Perner seized the opportunity given by the Danish government in 2007 that introduced a new law allowing acute tests on unconscious patients and, together with 32 colleagues, started the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial. The physicians randomly assigned 800 patients in intensive care units with severe sepsis and treated half of them with traditional crystalloid (Ringer's acetate) and the other half with the most commonly used engineered colloid, hydroxy-ethyl starch (HES).

Perner and collaborators found that after 90 days, more patients had died after being treated with hydroxy-ethyl starch than patients that were treated with Ringer's acetate – 51 percent versus 43 percent. Moreover, the starch-treated patients were not just more likely to die but also much more likely to have kidney failure or severe bleeding (*N Engl J Med* 2012 367:124). Bad news for the many patients around the world, who are still treated with hydroxy-ethyl starch.

Spot the difference

This was certainly also bad news for the producers of hydroxy-ethyl starch, like the pharmaceutical giant Fresenius Kabi. But rather than putting all their efforts into developing safer alternatives, they set their lawyers onto the scientists.

The colloid studied by Perner *et al.* was provided by Fresenius Kabi's competitor B. Braun: a product called Tetraspan with the specifications "HES 130/0.42". The corresponding starch product from Fresenius Kabi called Voluven is specified with "HES 130/0.4". A small difference! A relevant difference, though?

The product specifications are virtually identical. The first number specifies the average molecular weight of 130 kilodalton. The second number refers to the number of hydroxy-ethyl molecules per glucose molecule. "None of the companies can produce starches with that precision," Perner insists. And indeed, the indicated ranges are 0.38 to 0.45 for Fresenius Kabi's Voluven and, according to Perner, 0.40 to 0.44

for B. Braun's Tetraspan. It just happens to be a matter of the precision that the companies chose to indicate on the packaging and description of their products.

Law versus science

This, however, is not how Fresenius Kabi judged the situation. Actually, the company doesn't seem to consider "HES 130/0.4" as a scientific product specification but rather as a commercial number – or "HES number" as they say in the letter. For them, "[…] this error is misleading readers of the article and causing them to mistakenly attribute to the Voluven product the negative effects reported to have been found with Tetraspan, resulting in significant harm to Fresenius Kabi's reputation and economic damage through lost sales."

Therefore, Fresenius Kabi set an ultimatum of 48 hours for Perner to withdraw the article, change all references from "HES 130/0.4" to "HES 130/0.42" and include a statement that the previously-published article was incorrect. "If you do not agree, Fresenius Kabi AG is prepared to take all appropriate legal action to recover the economic losses it has suffered and will continue to suffer," they stated in their letter.

Interestingly, the drugs company itself does not actually consider this to be a threat, as their spokesman wrote in an email to *Lab Times*: "Fresenius Kabi did not announce to sue the authors of the article. Rather, Fresenius Kabi merely informed the authors that the article's title and text incorrectly identified the actually studied hydroxy-ethyl starch."

Prior to the "mere information" sent to Perner, Fresenius Kabi contacted the *New England Journal of Medicine*, whereupon the journal discussed the subject with the author. "We agreed that we did not want to change the manuscript," said Perner. After receiving the threatening letter, the physician gave in and corrected his purely legal errors in the article published on 27 June. The article was thus updated on 12 July followed by a formal correction in the journal on 2 August. However, Perner still maintains, "From a scientific point of view it actually makes no sense to be so precise."

That's a pretty good question...

Backfire effect

Despite the apparent victory of Fresenius Kabi, the whole matter has developed into a public relations disaster for the company. According to the Danish newspaper *Videnskab* that first wrote about the case, the Danish Medical Association denounced pharmaceutical companies that react with threats of compensation claims. In the same article the Rigshospitalet's medical director, Jannik Hilsted, called it an attempt to suppress academic freedom and also denounced Fresenius Kabi's "bullying methods".

It is thanks to a helpful source that *Lab Times* received the threatening letter sent to Perner. The Communications Department of the hospital refused to show the letter, stating that "due to our wish for a common good cooperative relationship it is not our intention to ask Fresenius Kabi for their consent". The drugs company, for its part, simply repeated statements made for earlier articles and ignored the request to prove them by showing the letter. In any case, Perner had a meeting with Danish representatives of Fresenius Kabi on 3 September, when they told him that the affair will not be pursued. Today, the physician says, "Overall, the case is settled."


Photo: University Hospital Copenhagen


Photo: Fresenius SE & Co. KGaA

Anders Perner versus Fresenius Kabi.
A dispute that makes no sense, scientifically.

The same but different

Leaving the legal nitpicking aside, Fresenius Kabi might indeed be right when they state in their letter that "although Voluven and Tetraspan have similarities, they are not bioequivalent". Voluven is produced from starch extracted from waxy maize, while Tetraspan is made from potato starch. The degree of branching of the glucose chains and the presence of esterified phosphates is higher in waxy maize starch. Also, in the end product the hydroxy-ethyls are not equally distributed in both products.

In their letter to Perner, Fresenius Kabi cited a study describing that both products are largely equivalent but Tetraspan is cleared faster from circulation than Voluven (*Drugs R D* 2007 8:229). However, when asked by *Lab Times*, Fresenius Kabi refused to indicate studies showing that Voluven is any safer or more efficacious than Tetraspan. The data of another 2008 study using a very different type of hydroxy-ethyl starch solution (HES 200/0.5) rather obtained very similar results to Perner's trial in terms of survival rates (*N Engl J Med* 2008, 358:125).

The debate goes on

The debate on the benefits and side-effects of the starch treatment, therefore, still continues. For Perner, it is clear that "the benefit of colloids for severe sepsis has only been shown in physiological experiments but never in patients". Whether colloids would still be useful in surgery and whether the natural colloid albumin performs better than hydroxy-ethyl starch, the physician leaves open. Prior to Perner's publication,

international guidelines for intensive care recommended using colloids (*Crit Care Med* 2008, 34:17).

However, there are also some scientists that are still not convinced by Perner's study. Nigel Webster, president of the Critical Care Medicine Section of the UK Royal Society of Medicine, told *Nature* magazine that trial participants who received starch were also given more blood products, such as plasma, than the people who received saline. This could affect outcomes. Other scientists, like Tobias Welte, pulmonologist at the Hannover Medical School, reproached in *ScienceInsider* that medial agencies have ignored evidence of potential side effects.

A systematic analysis of reviews between 1975 and 2010 found an overwhelming majority of 75 percent in favour of hydroxy-ethyl starch use. However, only twelve reviews performed meta-analyses and only seven of those were judged high-quality by an assessment questionnaire. All those seven did, in fact, recommend against hydroxy-ethyl starch use. The authors conclude, "Low-quality HES reviews reached different conclusions than high-quality meta-analyses from independent entities, such as Cochrane Reviews. The majority of these low-quality positive HES reviews were written by a small group of authors, most of whom had or have since established ties to industry." (*Intensive Care Med* 2012, 38:1258).

Gross scientific misconduct

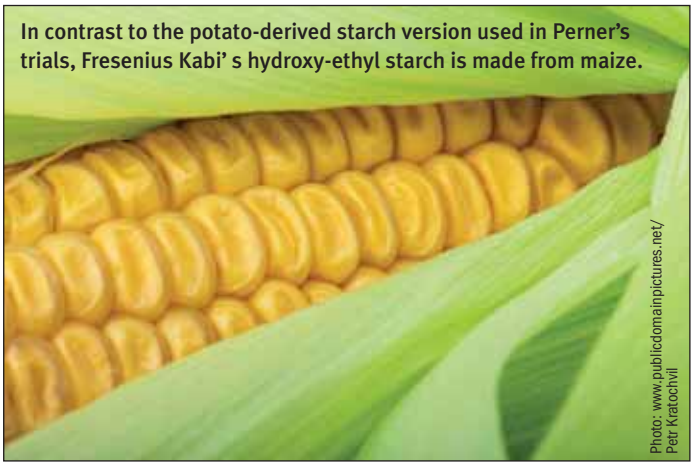
Biased reviewing not being enough, a good portion of research yielding results in favour of hydroxy-ethyl starch treatment has recently been found to be actually fraudulent and unethical. On 28 October 2010, the editor-in-chief of the journal *Anesthesia & Analgesia* retracted a paper by Joachim Boldt, a German anaesthesiologist at Ludwigshafen Hospital.

Shortly after the paper was published in 2009, readers found that the variability of some data was "too low to be believed". This finally turned out to be only the beginning of a record wave of 88 retractions of Boldt's articles because none of the completed studies had been approved by the responsible ethics committee. In addition, there was no registration made, no record of study files found and no informed consent by the patients obtained for many of the studies. On 9 August 2012, an investigation by the hospital formally concluded that in some articles even false data was published. Boldt himself had already been fired on 25 November 2010.

Ironically, Boldt's "glittering career built on charisma and charm", as the English newspaper *The Telegraph* described it, was also fuelled by industry. Boldt declared properly that "research activities have been supported by Baxter, B. Braun, Fresenius Kabi, Plasmaselect and Bernburg". Of course, this does not mean that any of these companies did encourage scientific misconduct. Still, Boldt's case is a big blow to them given that he was one of the most energetic advocates of their products.

Outdated authorisations

What now? Synthetic colloids have been developed since 1944; Fresenius Kabi entered business in 1974. Before the 1980s, the rules for the authorisation of drugs were less strict than today. Only in the aftermath of the scandal with thalidomide (tradenames Contergan or Softenon) that left many children with severe birth defects were the rules tightened. Irrespective of the change, new colloids were authorised based on old authorisations, which means that large scale clinical trials were never performed (*Swiss Med Wkly* 2012, 142:w13657).



In contrast to the potato-derived starch version used in Perner's trials, Fresenius Kabi' s hydroxy-ethyl starch is made from maize.

Photo: www.publicdomainpictures.net/ Petr Kratochvil

Despite this growing evidence of harm, colloids are still approved by the major regulatory authorities. While there has been concern about the compounds since 2001, the risk-benefit analysis has remained positive, the German medicine regulatory agency (BfArM) explained to *ScienceInsider*. At SwissMedic, a spokesman says, "We are in contact with the authorisation holders to discuss the safety signals and initiate according measures." The US-American Food and Drug Administration held a public workshop on "Risks and Benefits of hydroxy-ethyl Starch Solutions" on 6 and 7 September 2012. The workshop was informal and regarding the approval of hydroxy-ethyl starches, a consumer safety officer said, "Once the information has been fully evaluated, FDA will determine whether or not additional regulatory action is warranted and, if so, what action is appropriate. There is no specific timeline for this process."

The collaboration between scientists and companies is often an uneasy one – especially in the domain of medicine. While necessary to produce new and more effective drugs for society's health, the requirement to earn money by selling the products puts a lot of pressure on the companies and might well introduce a strong bias. However, not all companies are the same. Perner himself invited two companies to participate in his trial: Fresenius Kabi and B. Braun. Only B. Braun responded and thereby showed a good example – even if finally to their disadvantage. "B. Braun Melsungen were good collaborators. We unblinded the results with them," says Perner.

Waiting for more data

Fresenius Kabi, on the other hand, not only ignored Perner's invitation but later even complained in their threat letter that they were contacted by a regulating authority seeking a sepsis warning for their colloid product Voluven. The justification for not providing their product to Perner's 6S-trial and thereby avoiding any uncertainties was, as Fresenius Kabi's spokesman told *Lab Times*, that "a much larger trial in this field of research had already been planned". The study mentioned is the Crystalloid versus Hydroxy-Ethyl Starch Trials (CHEST) being performed in Australia and New Zealand. The CHEST-trial uses data of no less than 7,000 patients and is led by the George Institute in Sydney. The product: HES 130/0.4. Yes, 0.4 for sure!

The CHEST-trial is also the reason why regulatory authorities are still waiting to decide whether the authorisation status should be changed. The results were expected in August 2012 but have still not been published as *Lab Times* went to press. One of the sponsors of the CHEST-trial is Fresenius Kabi. Hopefully, no retractions and threat letters will result this time!

Florian Fisch