



Dear newsletter reader



Welcome to this year's first newsletter from Otsuka. We are looking forward to and expect an intensive year for our products: Adacolumn, Samsca and Pletal.

I am sure that nobody has been untouched by the tragic events in Haiti in the beginning of this year, and that many of us, either as a company or as an individual, felt the need to contribute. Our company donated 75,000 US dollars via the American Red Cross on a corporate level, and also

sent large quantities of our own nutraceutical products (health food and drinks) of a value of half a billion dollars from Japan. Although in a very sad context, it feels satisfactory to live up to our company commitment to be a good corporate citizen.

A rather unknown fact about Otsuka in Europe is our Art museum in Japan, housing thousands of reproductions of the world's most renowned masterpieces including the Sistine Chapel. You can read more about the Otsuka Museum of Art in this issue.

Happy reading!

Mari Liljefors
Communications Director
Otsuka Pharma Scandinavia AB



Tomato Hall at Otsuka Human Resource Center in Tokushima

How to challenge conventional wisdom: tomatoes must not necessary grow in soil! A tomato tree that grows in water produces from 8,000 up to 15,000 tomatoes a year, compared to soil rooted plants that only produces about 50-60 tomatoes a year.

What do you do when your IBD patients do not respond to pharmaceuticals?

Adacolumn is an apheresis treatment for patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis) which was launched in the Nordics in 2001. The Adacolumn device is a cylinder filled with beads of cellulose acetate. During the treatment activated leukocytes (granulocytes and monocytes) are selectively adsorbed to the beads and removed from the circulation. Until today, approximately 20,000 patients have been treated worldwide including approximately 1,000 patients in clinical studies. There are about 260 publications concerning the treatment of Adacolumn in IBD, which makes Adacolumn one of the best documented medical devices. A meta-analysis on six randomised controlled trials show significance in the effect of Adacolumn over control therapy.

At the recent ECCO (European Crohn and Colitis Organisation) IBD meeting in Prague, Italian experiences of Adacolumn treatment were presented. Between January 2008 and February 2009, sixteen GI units collected data from 154 UC steroid dependent/resistant patients. All patients were treated with Adacolumn according to standard protocols. The patients were evaluated by means of Clinical Activity Index (CAI), endoscopy and laboratory findings before treatment and after 3.5 and 12 months of follow-up. 65.3% of the patients were in remission (CAI<4) at 3 months follow-up. At 12 months of follow-up 82.7% of responders were still in remission.

In Läkartidningen no. 6, 2010 volume 107, leading gastroenterologists (Prof. Stefan

Lindgren, Malmö University Hospital MAS, Dr. Mikael Lördal, Karolinska University Hospital and Dr. Per Karlén, Stockholm South General Hospital) point out that it is reasonable to offer leukocytapheresis treatment as an option to patients where other established treatment options, including surgical treatment, have been exhausted. The authors conclude that treatment should, however, be focused on clinics which have a great deal of experience treating inflammatory bowel diseases.

Read the whole article in Läkartidningen no. 6, 2010 volume 107

or see the link from our web site www.otsuka.se/news.

For more information please visit www.adacolumn.net.

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You can subscribe to our Otsuka e-newsletter by sending an e-mail to: otsuka_news@otsuka.se (about 4 issues per year).



How do you treat hyponatremia?



Interview with Per Manhem, lecturer, chief physician at the Department of Endocrinology, Skåne University Hospital, Sweden.

Is hyponatremia common?

Low p-Na is the most commonly occurring electrolyte disturbance in hospitalised patients. P-Na <125 mmol/l causes a significant increase in mortality. In order to provide the right treatment, it is essential to clarify the cause. You have to try to determine whether the patient is hypovolaemic (e.g. loss of sodium via gastrointestinal tract), euvolaemic (SIADH) or hypervolaemic (e.g. heart failure, hepatic failure).

What problems do you encounter in the treatment of patients with hyponatremia?

It is essential to try to establish how rapidly the hyponatremia has developed, and whether any severe symptoms are present. It is probably not particularly dangerous to have chronic, low-grade hyponatremia, which gives the brain time to adapt to the lower sodium level. The patient generally has relatively mild symptoms such as dizziness, nausea, possibly some cognitive effects, etc. If the

patient is clearly symptomatic however, treatment must be initiated immediately. However, it can be dangerous to normalise the sodium level too quickly because you can then cause pontine myelinolysis, sometimes with fatal, irreversible cerebral damage with major consequences for the patient. The Swedish National Board of Health and Welfare's Department of Supervision of Health Services in Malmö has dealt with several Lex Maria cases, which relate to injury resulting from overly rapid correction of low plasma sodium values. The objective should be to raise the p-Na by a maximum of 0.5 mmol/hour, i.e. 8 - 12 mmol/L/24 hours. Rapid correction is only indicated in the event of serious symptoms, such as an epileptic seizure, unconsciousness and where the hyponatremia is relatively acute, i.e. it has arisen within the last 48 hours.

How do you treat a patient with hyponatremia?

If the patient is hypovolaemic, the water deficiency must be replaced with isotonic salt solution. If the patient is euvolaemic or hypervolaemic, the excess water should be reduced through water restriction for example, perhaps with the aid of a loop diuretic, and a vasopressin antagonist (vaptan), such as tolvaptan (Samsca), which can now be given perorally.

How do you diagnose SIADH?

You typically register tU-Na >40 mmol/l despite the patient having low p-Na and, euvolaemia (i.e. normal blood pressure, no orthostatism, normal skin turgor, etc.) is clinically registered. If you cannot await the test result for urine sodium and are uncertain of whether the patient is euvolaemic

or hypovolaemic, you can start by giving 1000 ml isotonic salt solution, for instance, over 4-8 hours, with measurement of p-Na after administering the infusion. A hypovolaemic patient will improve, with rising p-Na, while a euvolaemic patient will still have unchanged p-Na after infusion.

How does the clinic make use of tolvaptan (Samsca)?

Because we now know how the kidneys' water ducts function and the physiology of the effect of vasopressin has been clarified, the vaptan class of drugs has been developed to specifically act on the kidneys' V₂ receptors. By inhibiting the V₂ receptors, the vaptans cause an increase in electrolyte-free water excretion (aquaresis) and thus an increase in p-Na. This has given the clinic a specific treatment that directly addresses the physiopathological mechanism. Hopefully we will learn to use tolvaptan in the right way, resulting in improved safety compared with current treatments, where we are partially restricted to licence preparations such as demeclocycline.

Do you have any experience of Samsca?

Yes, but limited, as the drug has only been available on the Swedish market for a short time. This experience indicates that you achieve good aquaresis with obvious weight loss when using the drug.

For more information please visit www.samsca.se.

For complete product information, please visit www.emea.europa.eu/humandocs/Humans/EPAR/samsca/samca.htm

FACTS

SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion)

is a condition characterized by hyponatremia. It is often due to another underlying disease or a side effect of another drug. Hyponatremia in SIADH is due to inappropriate secretion of vasopressin i.e. increased secretion or sensitivity. This leads to increased reabsorption of water in the kidneys resulting in the dilution of p-Na (dilutional hyponatremia).

Vasopressin (ADH)

is a hormone produced in the hypothalamus and stored in the pituitary gland. It is secreted, in part through stimulation of osmoreceptors and baroreceptors and is of importance to maintain an adequate blood circulation. Vasopressin V₂ receptors stimulates reabsorption of electrolyte free water from the collecting ducts in the kidneys.

Samsca (tolvaptan)

is a vasopressin V₂ receptor antagonist that stimulates aquaresis or the increased renal excretion of free water, and thereby corrects the underlying cause of hyponatremia in SIADH.

Hyponatremia e-newsletter

We will soon introduce an e-newsletter with information related to Samsca, and the treatment of hyponatremia/SIADH.

You can subscribe to this e-newsletter by sending an e-mail to: hyponatremia_news@otsuka.se (about 3-4 issues per year).

Otsuka collects the art treasures of the world in one place

The Otsuka Museum of Art houses reproductions of the western world's greatest art treasures, brought together under one roof. Here you can discover works of art from 179 museums in 26 countries in a single afternoon.

The late industrialist Masahito Otsuka was concerned at seeing the art treasures of the western world crumbling away as a result of pollution, outbreaks of war and the ravages of time. When one of the group's subsidiaries succeeded in developing a technique for producing exact copies from photographs into ceramic tiles, the idea of preserving the greatest works of art for posterity in the form of extremely lifelike ceramic reproductions was born. Six art historians spent more than a decade obtaining the rights to reproduce these artworks. Picasso's heirs required lengthy persuasion, resulting in the museum proudly boasting the very first reproduction made of "Guernica" and reproductions of Picasso's entire output.

The first stage involves taking precise photographs of the work of art. These are copied onto silkscreens and attached to clay, which is then fired at a high temperature on several occasions. The reproduction is expected to last for more than 2,000 years, and is therefore preserved for future generations. Certain works are even stored in underground nuclear weapon- and earthquake-proof rooms.

Guernica is in good company with no fewer than 25 Goyas, 12 Rembrandts and 7 Van Goghs, as well as works by Andy Warhol and a full-size replica of the entire Sistine Chapel, to mention just a few of the more than 1,000 reproductions. An entire room is dedicated to Da Vinci's "The last supper" which is actually the only place in the world where you can compare the painting before and after its restoration. Following the great success of the book "The Da Vinci Code", the room has attracted a lot of attention. Sweden is represented with Sven Richard Bergh's "Nordic Summer Evening" and from Norway you can find several works by Edward Munch. The Danish artist Wilhelm Ham-



One of the museum's highlights is a full-size reproduction of the Sistine Chapel.

mershøi is also among the Nordic artists that are represented. However, there are no Asian works, as these can be seen at closer quarters. After all, the basic idea is to bring people closer to works of art that most of them would never have the opportunity to see in real life. Seeing the reproductions makes for a much more impressive experience than seeing the same works in art books and in illustrations.

The museum was opened in 1998 and is located in the small coastal community of Naruto on eastern Shikoku, Japan, which

was also Masahito Otsuka's hometown. The Otsuka Group celebrated its 75th anniversary in the same year.

More than 230,000 people visited the Otsuka Museum of Art last year. Even for those who have seen the original Mona Lisa, the opportunity to see the painting without glass protection, crowds and tight security is an experience in itself.

You can make a virtual tour of the museum by visiting www.o-museum.or.jp/english/.

Newcomers at Otsuka

Pontus Billstam, Business Unit Director, Pharma



– I was previously Business Unit Manager, Cardiovascular at Sanofi-Aventis. Otsuka is an expansive company which still has a family feeling, and where you have the opportunity to make a difference.

Tobias Helgesson, Finance and Administrative Director



– My previous job was Senior Business Controller at Sanofi-Aventis. – We will have both internal and external audits during the spring, so there is a lot to do. Also, I have about a thousand new things to learn.

Anna Juhlin, Quality Manager



– I was previously Quality Manager at Sanofi-Aventis. As Quality Manager at Otsuka, my role is to ensure that processes are in place for all regulated and key activities so that we comply with regulations and internal guidelines.

Susanna Holmgren, Account Manager Adacolumn in Stockholm, Mälardalen & Södra Norrland



– My previous position was Account Manager at Merck Serono. Otsuka is a very big company in Japan, and is currently growing in the Nordics. It is extremely interesting being part of this journey.

Hans Söderlund, Account Manager Pletal



– Before joining Otsuka, I was an independent pharma consultant. This spring we will educate over 200 general practitioners in intermittent claudication, in order to meet the demand for increased knowledge in this area.

Dan Henrohn, Medical Advisor



– I have just completed my specialist education in rheumatology and internal medicine at Uppsala University Hospital. I have also initiated my thesis in medicine.

– In less than 90 years, Otsuka - a family business – has through its own research, development and production managed to develop a world-wide multinational company including both medical devices and pharmaceuticals with the ambition to be in the forefront of several therapeutic areas. I find that unique.

Mia Rhodiner, administrative assistant (actually working part-time with Otsuka since 2008 while studying at university).



– Otsuka is an exciting company, as we have unique products that previously were not available on the market. It is rewarding to work with products that help patients with diseases that were previously difficult to treat, or even difficult to diagnose.

Zinita Rust, Launch Manager



– I was previously Market Manager for Cardio Metabolic Care at E Merck (Merck-Serono). Otsuka goes against the flow, and is expanding while many other pharmaceutical companies are cutting back.

– We are working hard launching Sam-sca (tolvaptan), the world's first oral vasopressin antagonist and I can assure you that we see huge interest in this product.

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