Foder Callers

CLINICAL DEVELOPMENT OF XYLOCAINE AS A LOCAL ANESTHETIC.

by

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I will start with showing some tables of anesthesia methods at the department of anesthesiology, Kaolinska Sjukhuset, the years 1941 and 1946, (Fig 1-2) the time span under which xylodaine was developed. As seen regional and local anesthesia was used in quite a large extent, around 30 % each of all anesthesias. Spinal anesthesia was at that time used even for upper abdomanial surgery. Local anesthesia was given, of course for infiltration anesthesia and for goiter operations, hernias and also for thoracoplastic under paravertebral anesthesia, The agent of choice was procain / etocain, novocaine/ in ½ - 2% solution. Procain had however a short duration and adrenaline had to be added, 10 drops of 1:1000 concentration procain to 100 ml solution. The solution had to be prepared just before the use, as it could not be stored. Toxic reactions could also appear, so there really wae a need for a new anesthetic, especially one with shorter latency, longer duration, lower toxicity and possibilities for storage with adrenaline.

Fig 1
Fig 2

Xylocaine was synthetized 1943 by Löfgren and among 67 derivatives number 30 was found to be the choice/ LL30/. It was given the name of /Xylocaine, which is a union of its most important raw-product xylidine and the general surfix of local anesthetics-"caine"

The first contact I had with xylocaine was in the spring 1943, when I shortly met a college, dr Kornerup, ophthalmologist at Karolinska Sjukhuset, who told me that one of his fencing frinds /Lundquist/ worked on a new local anesthtic at the chemical institution of Stockholm University. I was interested, but busy with my own thesis on circulatory and respiratory changes during ether and

intravenous anesthesia in rabbits. I said:" I first want animal e xperiments,which show the toxicity compared to procain". This was later done by Goldberg at the departnent of pharmacology of Karolinska Institute. Goldberg was the right man for this task, as he also was an expert on statistics.

Lundqvist then contacted an old schoolmate, Bengt Lagergreen, who also was a fencer. He was a medical student and had worked at my department for 3 months 1940, when I gave him some reprints on local anesthesia. Lundqvist asked Lagergreen if he had some books on local anesthesia. He gave Lundqvist my reprints and a German textbook on minor surgery: Künzels kleine Chirurgie. Lagergreen asked why do you want these books." The answer was: " I will tell you later." From now on Lundqvist started rather heroic to use himself as a guinea-pig and used 2% LL30 on himself on toes and fingers and even spinal anesthesia, incredible, but true.

In August 1943 Lundqvist called Lagergreen and said that a friend of his had synthetized a new local anesthetic. They had arranged a meeting with representatives from the drug company Pharmacia and asked if Lagergreen would come as their medical expert and demonstrate finger blocks on student volunteers, So he did and gave 5-10 blocks on the fingers and the result was demonstrated for the executives from Pharmacia. They got 2 weeks for decision, but Löfgren and Lundqvist never heard of them, At 12 oclock after the respite time Lundqvist called Lagergreen and said that Mr Jordan at the US legation wanted to meet them.Mr Jordan was attachee of science at the US embassy. Lagergreen went there with Heeren more as an interpreter. Mr Jordan offered right away 15.000 dollar for the takover, but nothing was decided. The gossip spread like a fire and soon CIBA, Roche and Bayer was out for this new wonder drug. Also ICI was interested and it is told that Löfgren went to London in the tail of a Mustang, which flew ball-bearings from Sweden to England by night during the war. However no decision was made. All this happened between August 23 to September lo 1943, when ASTRA bought the method and

with the aeroplane

patency. How this happened can also be told as a thrilling story, but I must now come to my own picture in this xylocaine drama.

I had earlier had close contact with ASTRA and it was natural that I was asked to handle the clinical investigation of xylocaine, Further I was the only anesthesiologist in Sweden at that time. The preliminary investigations on toxicity by Goldberg 1944 (Fig 3) showed that the toxicity of xylocaine was not greater than that of procain and I started the clinical investigations at Karolinska Sjukhuset 1945, We started with blind wheal tests. The different xylocaine solutions were tested parallel with procain and tetracaine. Each bottle was given a number so that the operator who made the test did not know what the bottle contained. All solutions were tested simultaneously on the same patient. Subcutaneous injections of 1 ml was given on the volar side of the forearm and the analgesia tested with the point of a needle. 175 tests were done and the result is seen in table 4.

No local reaction was observed in this series. If adrenaline was added in a concentration of 1:100.000 a considerable longer duration of analgesia was observed. Whereas 1% procain solution with adrenaline has a duration of 60-90 minutes, the analgesia produced by 1% xylocain with adrenaline lasted for 4-5 hours.

Wheal tests with intracutaneous injections of 0,1 ml were also made/Table 5 / No local reaction was observed in this series either, The wheal tests showed that xylocaine was definitely superior to procain concerning latency and duration and I never considered any statistical analysis necessary. In this investigation I had the assistance of a young physician, my wife Ulla, who also is present here, The volunteering patients were give 5 crown / 1 dollar/ for their help and the students were given the choice of a copy of my thesis/1945/ or a package of American cigarettes, which were very difficult to obtain during the wae. Most of them chose a package of Camel or Lucky Strike.

After this preliminary investigation I ~~went~~ to clinical anesthesia. At the out-patient department 400 registered anesthesias with ½, 1 and 2% solutions without adrenaline were recodded. Xylocaine could thus be given without adrenaline, which was expected according to the wheal tests. At the surgical operation department, where longer duration was ~~wantd 305 registered cases with~~ the addition of adrenaline 1:100.000 ~~were performed~~. Not more than 1 g was used, ~~thus 100 ml 1% or 200 ml 1/4%.~~ The anesthesias were given routinly as with procain for goiter operations, hernias and thoracoplastics. The usual conducting anesthesias as for mandibular block, brachial plexus, sacral and paravertebral blocks were ~~used~~. In therapeutic anesthesia xylocaine was of great value for its long duration/6-7/.

Xylocaine was ~~also~~ tried in spinal anesthesia where 2% in 10% glucose gave ~~a fast and~~ sufficient anesthesia in the lower segments.
Alsoxasxxxsurfacexanesthesiaxxylocainexwasxeffectivexinxthexeyexandxxx thexlarynx Xylocaine, unlike procain, also showed to be surface analgesic on the cornea, the throat, larynx and trachea and was used in 2% solution for intubations and bronchoscopy. It was also used for topical anesthesia in urology. ~~Toxic reactions was provoked by me and their treatment showed to be the same as for procain.~~

During this clinical investigation xylocaine was simultaneously tested by a number of dentists in dental anesthesia with excellent results/ Björn,Hult,Bremer.Ekmanner.Persson and Strandberg/ Fig 6 shows the efficiency values for various solutions compared to procain, The anesthesia was studied with the aid of an electric stimulator according to Björn.

The first presentaion of our clinical results was done at a meeting of the Swedish Anesthesia Club 1947 / The Swedish Society of Anesthesiologists /1950/ See Fig 7. The same year it also was presented at the Scandinavian Surgical Societyes first meeting after the war in Stockholm. The results ~~was~~ published in Svenska Läkartidningen 1948 and xxxxxxxxxxxxxxx ~~The first appearence abroad~~ xxxxxxxxxxxxxxxxxxxxxxxxxxxxcame 1949 in Anesthesxxxxx

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quote:

In the summary I ~~say that~~ the introduction of a new local anesthetic is only justified if it ~~owns~~ has advantages ~~against~~ before already accepted drugs. The experience hitherto show, that we in xylocaine have got a drug with such qualifications. It will fullfill the classical requirements for an ideal ~~drug~~ local anesthetic, as it has low toxicity, is not tissue irritating, is water soluble, can be sterilized and permitts storage with adrenaline. Xylocaine has further a fast and efficient ~~effect~~ effect with long enough duration and is according to my opinion the most ideal of hitherto known local anesthetics. It is further remarkable useful within all areas, where any form of local anesthesia can be used."

Fig 8

Fig 9

Fig 14

The same year Löfgren presented his thesis on xylocaine/Fig 8, 9/ which rendered him the highest point. 1949 the first publication abroad of the clinical results appeared in the British anesthesia journal Anesthesia /Fig 10/ and the same year I write in the Swedish year book Medicinska Framsteg/Progesses in Medicine/ " This entierly Swedish preparation is now paid attention to all over the world. Maybe this triumph for Swedish chemical-anesthesiological research will show itself to be the greatest progress in local anesthesia since the introduction of procain/etocain,novocaine/

To one who took part in the pioneering research in the pharmacological and clinical action of xylocaine ,it is gratifying to find that the original observations, maybe simple according to modern requirements, stands up so well when appraised in the light of later findings and critiques. In the last analysis only long documentated fitness for use ~~experiences~~ can assure the survival of a drug. Xylocaine has for more than three decades stood the test as a reliable and highly efficie local anesthetic.

Supplemental Digital Content 4:

Notes for a lecture given by Torsten Gordh given at the American Society of Regional Anesthesia in 1985.