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Round table discussion

Future programs in the basic and clinical sciences on surfactant stimulation and substitution

Moderator: Michael Obladen

OBLADEN: The first problem we should approach is the surfactant researcher's fear: Is my material the right stuff? Dr. HALLMAN, should an exogenous surfactant contain protein, and which protein?

HALLMAN: Right now we have two types of apoproteins, one is the 34 KD, which is not lipid soluble, but contains many hydrophobic and hydrophilic portions and also some collagen-like structures. Then there is the low molecular proteolipid that seems to enhance the adsorbtion of surfactant. It makes the adsorbtion of synthetic phospholipids remarkably faster when we add the proteolipid.

MORLEY: I have presented results today, that an artificial surfactant which contains no apoproteins has beneficial effects. I think apoproteins can be found in association with surfactant. Their exact function still remains to be demonstrated. It may be, that our surfactant mixes with apoproteins present in the trachea.

ENHORNING: Dr. MORLEY, to be honest with you I think there is a problem with your artificial surfactant that its adsorbtion rate is very low. And I think this is the reason why you don't see the immediate effect. The long term effect, lowering the mortality, probably is due to recirculation of the phospholipids you have introduced. My feeling is an advantage of giving surfactant before the first breath. If you give it later on, there is already damage to the airway and subsequent protein leakage.

SAUGSTAD: I feel, Dr. MORLEY's data would be different with something else than saline as placebo. We have now data on the newborn rabbit showing that there is a clear dose response relation between saline volume and decreased compliance. And as I understand, Dr. MORLEY gives up to three ml of saline in the first hour to the control group.

MORLEY: Having seen the data that other people have produced, I probably would not use saline for control any more. However, if one thinks to pour two ml of saline down the trachea is harmful, neonatologists around the world need to rethink tracheal toilet as a lavage, because well over 75% of the neonatal units in England use approximately one ml of saline for tracheal toilet. The fact is that there is saline in our surfactant. If saline per se is harmful and our surfactant was a suspension, then equal effects should have come from the saline mixed in the surfactant.

OBLADEN: We also should speak about side effects. Circulating antibodies have been demonstrated and they have not only been demonstrated after treatment with material of animal origin. They even have been demonstrated after RDS without any supplementation. I would like to ask Dr. HALLMAN and Dr. ENHORNING to comment on the potential significance of immunization due to administration of exogenous proteins.

ENHORNING: If you give only one dose and give it to very preterm infants with a poor immunological response, I don't think you have to worry much. Furthermore, these infants are fed cow's milk and certainly they very often inhale some of the milk. So there is a chance of getting the antigen down the airways even if you don't give surfactant.

HALLMAN: I agree completely. It is very unlikely that there are serious immunological side effects. Dr. STRAYER, who is an expert in immunology, has measured immune complexes and also specific immune complexes. They were not increased by human surfactant.

WEITZEL: Dr. HALLMAN, you have shown a reduction of CH 50 activity or even C 3 activity, and I guess you used a plate test?

HALLMAN: We have also been using C 13 and we compared surfactant versus placebo and didn't see any difference.

ROOTH: You have a tremendous vascular dilatation when Pco_2 is up in the beginning of RDS and so the stage is set for disastrable side effects. You are speaking of the immediate effect of saving the lungs, but I think we also have to look into the future and to consider the reactions of the brain.

OBLADEN: I think everyone who has been doing rescue studies has observed relapses. I would like to ask those people who have done prevention studies: Do you see relapses?

HALLMAN: Well, first of all it is a matter of dosage. We formerly used 60 mg and now in the new trial went up to 80 mg. With this dosage and with really sick immature babies we do see a relapse, and I would almost say that you can use anything, you will see relapse in any surfactant. Right now, our policy is not to wait for the relapse: We are aggressively giving more, if it looks like that the baby does not go close to 21% of oxygen. And if the baby's chest still doesn't move, we give more.

OBLADEN: Nearly every researcher uses different success criteria in his study. Dr. HALLMAN, if I would squeeze you now to restrict yourself to three success criteria and not look for any more than just these three, which three would you pick?

HALLMAN: Long term death and overall BPD incidence. Then there would be ventilatory index which would include mean airway pressure, FiO_2 and Po_2.

OBLADEN: Dr. MORLEY, you measured compliance and you explained to us compliance is difficult to measure. In some infants it is not possible to measure it at all.

MORLEY: Measuring compliance of these tiny babies is extremely difficult and extremely unreliable. I do not put great faith in the absolute compliance measurement for each baby.

OBLADEN: Could we speak a little about the group of infants who are non-responders? Do you see them?

MORLEY: Yes, we see non-responders. Quite a lot of our non-responders are babies who are too mature to respond. They are doing well anyway.

ENHORNING: In a rescue study we saw one non-responder out of six. But this was severely affected by RDS when the surfactant was given, the baby was severly damaged in his airways. Furthermore, there were practical problems in instillation of the surfactant in that case. It probably never came to the trachea.

HALLMAN: We have a total of four non-responders, two are in a rescue study and two in a prophylactic study. I would prefer to talk about poor response. The problem is, you are treating them already with very high pressures, you give surfactant, you get an increase in oxygen, but you cannot go down with the ventilator pressures and at autopsy they may have massive hyaline membranes.

OBLADEN: The next point is future: What to do when to plan a study? To which gestational age should it be restricted? Which material should be taken? How should it be dosed? How often should it be given? Should both rescue and prevention studies be performed? Pilot versus control versus blind versus deaf? Every experienced nurse using a stethoscope will immediately hear if a baby has received surfactant or not. Should the controls be bagged, should they remain untreated, should they receive placebo?

ENHORNING: The lower the gestational age, the greater the chance to find an effect with a limited number of cases. In prevention studies you have a better chance to see an effect, but there is a need for rescue studies too, no question. I think pilot studies on surfactant supplementation are not tolerable any more, because it is too clear that it works. Of course studies should be controlled and should be blinded as far as you can. Saline for the controls is not justified because you might put your control in a worse situation.

OBLADEN: I will try to sum up what we have heard: Surfactant supplementation cannot be termed as standard clinical treatment but must be performed on an investigative basis. For prevention studies, we will need several hundred infants below 30 weeks' gestation for significant results. We need a close look on side effects. It is still open if surfactant supplementation contributes to ductus arteriosus, to lung bleeding, to intraventricular hemorrhage and to circulatory disturbancies. It would be very valuable if common endpoints could be found to make the different published studies more comparable to each other. I think it is

not ethical any more to perform supplementation studies with a no-treatment group. Instead, the time has come to compare different surfactants with each other.

Prof. Dr. Michael Obladen
Department of Neonatology
Children's Hospital
The Free University of Berlin
Heubnerweg 6
D-1000 Berlin 19, West Germany