

SUMMARY MINUTES

OF THE

NEUROLOGICAL DEVICES

ADVISORY PANEL MEETING

OPEN SESSION

November 16, 2000

**Potomac Rooms II and III
Quality Suites Hotel
3 Research Court
Rockville, MD**

**Neurological Devices Advisory Panel Roster
November 16, 2000**

Alexa I. Canady, M.D.
Neurological Surgery
Chairperson

Everton A. Edmondson, M.D.
Neurology
Voting Member

Richard G. Fessler, M.D., Ph.D.
Neurological Surgery
Voting Member

Robert W. Hurst, M.D.
Interventional Neuroradiology
Voting Member

Gail L. Rosseau, M.D.
Neurological Surgery
Voting Member

Cedric F. Walker, Ph.D., P.E.
Biomedical Engineering
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Regulatory Affairs and Clinical Research
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Consultant, Neurological Devices Panel

Thomas G. Brott, M.D.
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Andrew Ku, M.D.
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James C. Grotta, M.D.
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Justin A. Zivin, M.D, Ph.D.
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FDA Participants

Janet Scudiero, M.S.
Panel Executive Secretary
Division of General, Restorative, and Neurological
Devices (DGRND)

Celia Witten, M.D., Ph.D.
Director, DGRND

Stephen P. Rhodes, M.S.
Chief, Plastic and Reconstructive Surgery Devices Branch, DGRND

Janine M. Morris, M.S.
Senior Reviewer, DGRND

OPEN SESSION—NOVEMBER 16, 2000

Panel Executive Secretary Janet Scudiero called the meeting to order at 10:00 a.m. and read the conflict of interest statement. It stated that waivers had been granted to Kyra J. Becker, M.D., Richard G. Fessler, M.D., James C. Grotta, M.D., and Justin A. Zivin, M.D., Ph.D. and that these waivers allowed their full participation. Matters involving James C. Grotta, M.D., Everton A. Edmondson, M.D., Cedric F. Walker, Ph.D., P.E., Kyra J. Becker, M.D., and Justin A. Zivin, M.D., Ph.D. had been considered but were deemed unrelated to meeting and their full participation was allowed.

Panel Chairperson Alexa I. Canady, M.D., introduced herself and stated that the panel would make recommendations to the Food and Drug Administration (FDA) on the design of clinical trials for devices to treat and prevent stroke and for devices to provide neuroprotection by cooling. She noted that the panel members present constituted a quorum and asked them to introduce themselves.

PANEL UPDATE

Stephen P. Rhodes, Chief, Plastic and Reconstructive Surgery Devices Branch, Division of General, Restorative, and Neurological Devices (DGRND) updated the panel on matters since the last panel meeting. The Cordis Trufill Cyanoacrylate premarket approval application (PMA) for arteriovenous malformations (AVMs) was approved on September 25, 2000. The draft Neurological Embolization Guidance Document was revised in accordance with the panel's recommendations made at its September 1999 meeting and public comments and is now available on the FDA web page. The panel's September 1999 recommendation to reclassify the totally implanted spinal cord stimulators from class III into class II was published in the *Federal*

Register this September. Mr. Rhodes announced the following four FDA personnel moves: Mr. James Dillard is now the Director, Division of Cardiovascular and Respiratory Devices (DCRD); Mr. Mark Melkerson is now the Deputy Director, DGRND; Dr. Russell Pagano has moved to DCRD, and Dr. Diane Mitchell is now Acting Chief, Restorative Devices Branch.

Mr. Rhodes introduced **Dr. Bernard Statland, the new Director of the Office of Device Evaluation.** Dr. Statland thanked the panel in advance for their recommendations on this meeting's timely issues. He presented letters and certificates of appreciation to outgoing Panel Chairperson Dr. Canady and outgoing panel members Everton A. Edmondson, M.D., Anne W. Wozner, Ph.D., R.N., C.C.R.N., and Sally L. Maher, Esq.

FDA PRESENTATION ON PREVENTION AND TREATMENT OF STROKE

Janine Morris, M.S., Senior Reviewer, DGRND, stated that the purpose of this meeting was to address the important issues of acute ischemic stroke and hypothermia for neuroprotection. The FDA is seeking the panel's recommendations on how to clinically study emerging device modalities for the treatment and prevention of acute ischemic stroke and of cooling devices for neuroprotection in their respective targeted patient populations.

Ms. Morris presented FDA's perspective on the emergence of endovascular therapies for the prevention and treatment of acute ischemic stroke. She noted that the specific focus of the day's discussion was the clinical trial design considerations regarding potential endovascular therapies of the intracranial arteries in the prevention and treatment of ischemic stroke. Ms. Morris reported that atherosclerosis of the major intracranial arteries is an important cause of ischemic stroke. Treatment of patients with

symptomatic intracranial atherosclerosis falls into two categories: prevention of recurrent events in patients with a completed stroke or resolution of transient ischemic attacks (TIA) and treatment of acute ischemic stroke. Current medical intervention to prevent ischemic events is medical antiplatelet therapy. Endovascular treatment of coronary and peripheral atherosclerosis, including stenting and percutaneous transluminal angioplasty (PTA) is now widely used in these arteries. As a result of the successes in the cardiovascular disease, these cardiovascular device designs are being modified for the intracranial artery disease. The clinical literature is now reporting the use of stent and balloon placement in the intracranial arteries using modified stents, catheters, and delivery systems.

The second broad category of treatment of patients with symptomatic intracranial atherosclerosis is the treatment of acute ischemic stroke. The only currently FDA-approved treatment of acute ischemic stroke is the intravenous delivery of tissue plasminogen activator (tPA). The literature has described interest and attempts to use various endovascular methods, such as laser thrombolysis devices, mechanical thrombectomy devices, and other physical means of disrupting a clot. As these devices are being developed, new treatment paradigms, including some combinations of mechanical thrombectomy or thrombolysis (PTA) and stenting are evolving. Early consideration of the regulatory process to evaluate the safety and effectiveness of these devices should address clinical trial issues, such as patient populations, clinical endpoints, timing of treatment, combination therapies, and control populations. Ms. Morris then read the five questions for panel discussion.

OPEN PUBLIC HEARING

Christopher M. Loftus, M.D., F.A.C.S., University of Oklahoma College of Medicine, spoke on behalf of the **American Association of Neurological Surgeons and the Congress of Neurological Surgeons.** He noted that the prevention of recurrent events and the treatment of acute ischemic stroke are two very different questions that require different study designs. For prevention of recurrent events, he recommended that symptomatic patients should be studied first to prove efficacy, that the study design should be endovascular treatment with best medical therapy versus best medical therapy alone, and that the technology should be stabilized before embarking on a clinical trial. Assessment of complications should include wound complications and TIA/stroke/death within 30 days; endpoints should be TIAs and stroke/death with at least five years of follow-up.

For treatment of acute ischemic stroke, Dr. Loftus suggested that evaluation of extracranial endovascular procedures could potentially be a three-arm trial of endovascular plus best medical therapy, best medical therapy and acute surgical intervention. Because there is no standard surgical strategy for intracranial procedures, a medical/endovascular randomized trial design would be better for intracranial procedures. Trial design should use tPA data as the “gold standard,” and entry criteria must replicate tPA criteria for time from stroke and neurological assessment, which will disqualify many patients. Technology must be stabilized and reproducible, and interventionists must be certified. Assessment of complications would be similar to the first study, but endpoints would be immediate or early neurological improvement (hourly and daily), as well as the negative endpoints of no complications, TIA, stroke or death within 30 days. Assessment by neurologists should be done every three months for both trials. Both treatment and

prevention trials should use an intent-to-treat analysis, should be randomized but not blinded, should have no crossovers, should use certified interventionalists, and could have blinded follow-up.

J.J. Connors III, M.D., INOVA Fairfax Hospital, read a statement from the **American Society of Interventional and Therapeutic Neuroradiology (ASITN) and the Society of Cardiovascular and Interventional Radiology (SCVIR)**. The societies believe that the results of the PROACT II trial are convincing evidence that intra-arterial thrombolytic therapy can now be considered an acceptable and appropriate therapy for acute stroke. Dr. Connors stated that active intervention for emergency stroke treatment is appropriate and justifiable. He noted that the primary endpoint for a device should be that it does its intended function, and that no stroke treatment device should be approved without appropriate attention to patient outcome. Concurrent stroke patients enrolled and evaluated at other institutions that do not participate in interventional rescue might be one possibility for controls, as might the use of historical controls. Dr. Connors discussed the Interventional Stroke Therapy Outcomes Registry (INSTOR) as one method of data collection. He encouraged the combination use of experimental devices with investigational drugs, approved drugs, or off-label uses of drugs in study design.

Helmi L. Lutsep, M.D., spoke on behalf of **the Oregon Stroke Center**, which is involved in the design and execution of mechanical thrombolysis device studies for the treatment of stroke. They strongly recommended use of historical controls because they believe that placebo treatment is unethical for needing intra-arterial treatment and there is no approved treatment after the three-hour window for tPA treatment. They recommended recanalization rates for the primary outcome measure and clinical efficacy

measures for the secondary endpoint. Because angiography provides objective imaging data, other radiographic outcome measures are not necessary. They also recommended that consideration be given to inclusion of patients with occlusions in other vessels, in addition to the enrollment of patients with MCA strokes.

Alexander M. Norbash, M.D., of Brigham and Women's Hospital, discussed the following three types of endovascular stroke therapy and presented representative case reports illustrating their use: conventional treatment with catheters and thrombolytics, unconventional treatment with balloons, and an avant garde approach of using snares and other mechanisms. With respect to trial design, he recommended that historical controls be considered to allow sufficient numbers of eligible candidates, rigid safety standards to avoid complications, and rigid benchmarks for *in vitro* testing. He also recommended that recanalization be considered a primary endpoint and that distal clot embolization be considered potentially acceptable.

Mark J. Alberts, M.D., of the Duke University Medical Center, discussed opportunities and challenges in carotid stenting for cerebrovascular disease, listing possible advantages of carotid stenting, such as fewer complications, lower costs, and less invasiveness. He presented preliminary results of the Schneider WALLSTENT prospective, randomized trial of carotid stenting versus carotid endarterectomy in patients with symptomatic stenosis. The study was terminated early because a futility analysis showed no chance of proving the equivalence hypothesis. The trial raised other issues, such as whether a longer training period could reduce complications and whether newer stent devices might reduce complications. Dr. Alberts presented worldwide stenting data on 4,757 patients from 36 centers that showed technical success in 98.4% of cases, with

low restenosis and complication rates. He discussed key aspects of stent utilization in patients with cerebrovascular disease, such as patient issues (selection, symptoms, and risk/benefits), personnel issues (multidisciplinary teams and expertise), device safety and effectiveness, concomitant medications, and procedure techniques and monitoring. Dr. Alberts' recommended that only well-trained physicians to perform stenting for cerebrovascular disease, having a multidisciplinary team screen patient selection, independent neurological monitoring to evaluate complications and long-term results, and tracking all patients through a national registry. He also recommended that all patients have a diagnostic four-vessel cerebral angiogram prior to stenting, that manufacturers develop evidence on device safety and effectiveness in the cerebral vessels, that trials use a standard post-stent protocol, including neurological exams and neuroimaging studies, and that they report 30-day and one-year results.

INDUSTRY PRESENTATIONS

Ajay Wakhloo, M.D., Ph.D., from the University of Miami School of Medicine spoke on behalf of **Medtronic AVE-Neurological Technologies** on the role of intracranial stenting for treating atherosclerotic lesions and intracranial aneurysms. He said that for atherosclerotic lesions, stenting is a minimally invasive approach that improves the efficacy for intracranial vessel repair and enhances safety by reducing subacute thrombosis, and he presented a case study. He listed appropriate patient indications (symptomatic intracranial atherosclerosis without total occlusion while under medical therapy or asymptomatic high-grade stenosis), appropriate controls (medical management and interventional management), and clinical outcomes and endpoints (recanalization of intracranial arteries determined angiographically without a deficit in

neurological function or death/stroke rate and stroke severity), and recommended efficacy follow-up at one to three months, plus safety follow-up for six months.

Dr. Wakhloo stated that stenting for aneurysms is an adjunctive measure aimed at improving the efficacy of current therapy. He suggested patient indications (inoperable cerebrovascular aneurysms or those unsuitable for conventional therapy alone) and safety and efficacy endpoints (no worsening of neurological conditions and prevention of coil migration) be determined at six months, with follow-up for 12 months. He concluded that neurovascular stenting presents advantages over current interventional therapy for intracranial aneurysms and atherosclerotic lesions because it provides a platform for biomechanical and local hemodynamic repair and healing of diseased neurovasculature.

Jim Gustafson of Possis Medical, Inc. discussed investigational device exemption (IDE) clinical trials for device-mediated stroke treatments. Based on his company's experience with their AngioJet Thrombectomy Catheter System for removal of intravascular thrombus, he reviewed considerations involving controls, multiple treatments, and outcome measures. Mr. Gustafson noted the difficulty involved in randomized controlled trials for stroke treatment and suggested that controls could be based on objective performance criteria (OPCs) found in the literature, using a smaller study overall with the same statistical power. Because new modalities are not limited to the three-hour treatment window, these may be more realistic to the eventual clinical setting. He acknowledged that investigators want to use multiple treatments concomitantly, which may confound evaluation of the investigational treatment. Challenges include whether the trial design can forbid concomitant treatments or separate treatment effects. If concomitant treatments are allowed, he asked whether the approved

indication must specify use concomitant with other treatments, and what should be done about off-label concomitant treatments. For outcome measurers, he recommended that the primary endpoint of recanalization devices should be angiographic evaluation of the immediate treatment effect on the lesion seen at presentation.

Lee Schwann, M.D., of Massachusetts General Hospital, spoke on behalf of **Boston Scientific/Target Therapeutics, Inc.** on trial design considerations in use of stents to treat symptomatic intracranial atherosclerotic disease. On patient selection, he noted that patients with posterior circulation stenosis who fail medical therapy are often removed from randomization because of their poor prognosis but actually are ideal candidates for a novel intervention. He proposed definitions for failure of best medical therapy, such as recurrent ischemia despite therapy, therapy intolerance, or serious adverse events. On control group selection, he asked whether it is ethical to randomize patients to continued medical therapy after they have failed it and whether patients can be retained in the medical arm of a randomized prospective device trial when the intervention is available off label. He also asked whether there are enough data to support a historically controlled, single-arm trial design. For outcome assessment, he recommended conventional measures, such as functional outcomes at six months, incidence of major versus minor stroke, adverse events, complications, risk of hemorrhagic complications over years of anticoagulation, and impact on quality of life due to continuous warfarin management. Dr. Schwann noted that potential bias could be a problem, given enrollment of the highest risk patient group, and could also result from customary, off-label use of concomitant therapies and advances in antithrombotic therapeutics over the next few years.

Charles Strother, M.D., of the University of Wisconsin—Madison Medical School, spoke on behalf of **Endovascular, Inc.**, on acute stroke therapy. He noted that large randomized trials have demonstrated that treatment can improve outcome of stroke if patients are treated up to six hours after onset, and comparison to those trials requires a six-hour time limit after onset or separate studies for those at more than six hours. On imaging, he thought CT is the key for detection of hemorrhage and patient exclusion, although MRI could be useful after the six-hour limit in selecting those who will still benefit from therapy. Dr. Strother stated that historical controls allow access to a well-studied placebo control group for technical and clinical endpoints. Regarding outcome measures, safety is the primary concern, with vascular injury likely the greatest risk. On efficacy, Dr. Strother thought that stroke will eventually be managed with a combination of therapies designed to address different aspects of the disease, each of which should be tested against appropriate technical endpoints. For recanalization devices, the endpoint would be flow in the occluded artery as measured on an angiogram. Secondary endpoint data on clinical outcome are important, and the endpoints of the PROACT II trial should become standards for device studies.

Ajay Wakhloo, M.D., Ph.D., spoke again, this time on behalf of **Cordis Neurovascular, Inc.** on protocol design for endovascular therapy for intracranial atherosclerotic disease. He recommended that the primary objective should be evaluation of the safety and effectiveness of **PTA define**/stenting to treat intracranial atherosclerotic artery stenoses. Safety endpoints should be evaluated at 30 days and six months post-procedure and should include the incidence of stroke and neurological outcome measures. Effectiveness endpoints should be angiographic outcomes post-procedure and at six

months. He outlined inclusion and exclusion criteria for the study population and discussed the nature of atherosclerotic disease. Dr. Wakhloo concluded that the new generation of stents could be used for three different diseases: atherosclerotic diseased segments of intracranial vessels to prevent cardiovascular atherosclerosis (CVA), acute arterial occlusions, and complex aneurysms of anterior and posterior circulation. The major issue will be long-term complications.

OPEN PANEL DISCUSSION

Dr. Justin Zivin, Consultant on FDA's Peripheral and Central Nervous System Drugs Advisory Committee, as the lead panel reviewer, addressed the panel. He reviewed demographics on stroke and stroke risk factors, which include both unmodifiable and modifiable risks, and stroke mechanisms. Dr. Zivin outlined proven specific therapies, both medical and surgical, and trial designs for prophylaxis, such as most stenting trials, and acute treatment (thromboembolytics).

Dr. Zivin reviewed inclusion and exclusion criteria for device trials, including the age of patient, medical conditions, concomitant medications, stroke mechanism subtypes, and time since onset. Endpoints for prophylaxis trials include recurrent stroke and death; for acute treatment they include use of stroke assessment scales, such as the Barthel Index, the NIH stroke scale, the modified Rankin scale, and the Glasgow outcome scale. Dr. Zivin showed the scale results as shown in the NIH t-PA trial, noting that the scales all worked equally well as outcome measures. He recommended use of either the Glasgow or Rankin scales.

On use of surrogate markers, Dr. Zivin disagreed with previous speakers who argued for measurements of blood flow or vessel patency or lesion volume as endpoints,

saying that such endpoints are poorly correlated with neurologic function and have not been proven useful for stroke.

Dr. Zivin summarized the following three lessons learned from thrombolytic development programs: three-hour treatment window for tPA will change the standard of care and improve recruitment in short-time window studies, the use of a stroke team facilitates successful treatment, and protocol concerns can dilute or obscure treatment effects. He refuted the concerns that have been voiced about use of tPA for stroke therapy (ineffectiveness, danger, or inconvenience), saying that most have been discredited but may still cause controversy for trial designs and its use. He listed failures in neuroprotective drug development programs, noting the difficulty of developing such effective treatments.

On the FDA questions, Dr. Zivin recommended that patient populations exclude those with hemorrhages and small vessel strokes and include ischemia subtypes predetermined in phase I and II trials, as well as protection from embolization during surgery. Surrogate markers, in his view, may be useful for patient selection but are unacceptable for primary outcome measures. On controls, he argued for inclusion of add-on designs, which he saw as the only ethical course. Thrombolysis should take place less than three hours after onset, with a placebo acceptable more than three hours after onset in acute trials, and prophylaxis should include best current medical and surgical management.

Dr. Zivin said that several acute therapy rating scales have been proven useful as safety and efficacy outcome measures. Stroke and/or stroke-related death are conventional outcomes for prophylaxis, but transient ischemic attacks should not be used.

On confounding factors, Dr. Zivin recommended that concomitant medications should not interfere with devices, aside from anticoagulation that can be stopped temporarily, and combinations with proven treatments should be required. Acute treatment effects are usually measured at three months but could be measured sooner, given that most spontaneous recovery occurs within one month. Prophylaxis effects generally require several years of follow-up, although a number of trials have been stopped early.

Panel Deliberations and Discussion of FDA Questions

During general discussion, the panel debated the use of radiographic versus clinical endpoints, with some arguing that the endpoint must be clinical and others suggesting that MRI imaging of reduction in lesion volume may show some clinical validity. The use of transcranial Doppler to measure reocclusion was suggested as a non-invasive method worthy of exploration. The panel then proceeded to respond to the five FDA questions.

1) What characteristics should be considered in defining the appropriate patient populations for each respective treatment modality? What specific inclusion and exclusion criteria should be considered? What specific patient groups or subgroups should be assessed? What is the role of imaging techniques used to diagnose and assess stroke in describing the patient population for a trial?

For acute treatment, the panel agreed that only symptomatic patients should be included in the patient population, with treatment within a three-hour time period, although there was some sentiment for a six-hour time period. A sub-population cohort might look at treatment beyond the time limit. Two other patient groups that might be assessed separately would include those with Moya-Moya disease and those with anterior

versus posterior circulation stenosis. There was no sense of restriction on region other than the intracranial area. The sense of the panel was not to exclude intravenous tPA patients but to add these patients as a cohort. The panel saw the role of imaging techniques in acute treatment as helping, in combination with clinical outcomes, to assess recanalization or reduction in lesion volume. Such techniques are also very important to show the location and extent of the clot. The panel disagreed on the usefulness of diffusion-weighted imaging data.

In discussing preventive treatment, the panel agreed that there really is not a preventive arm because patients ought to be symptomatic to be treated. Patients should be in the acute treatment arm or have failed best medical treatment.

2) Discuss what characteristics should be considered in defining the appropriate control population for each respective treatment modality.

For the acute modality, the panel agreed that the control group patients should be those treated current medical treatment within three hours with tPA. It was suggested that data could be stratified into best medical treatment of tPA within three hours or best medical treatment after three hours, such as aspirin and antithrombolytics. The panel was split on whether the second post 3-hour group could have a historical control. It was suggested that there be a second analysis in the cohort, with and without tPA. The panel agreed there was no longer a preventive modality to discuss.

3) What considerations need to be incorporated when identifying appropriate outcome measures to establish safety and effectiveness? What secondary safety and effectiveness measures should be assessed?

The panel agreed that the major outcome measures to establish safety are death, stroke, perforation, infection, stenosis at the site, and injury to vessels. Major outcome measures for effectiveness are the dual endpoints of clinical outcome and recanalization. Vessel reopening is an important endpoint but not the primary endpoint.

In response to a question from **Celia Witten, M.D., Ph.D., Director, DGRND**, on how to measure angiographic success for both endpoints, the panel replied that ways to measure degree of recanalization have already been established in restenosis trials. Other secondary safety endpoints are hospital costs, quality of life, wound complications, and complications of angiography.

4) What sources of bias and confounding factors should be considered in study design?

How should combination therapies be considered with respect to trial design? How should concomitant medication be considered in the trial design?

The panel agreed that the design of such studies presents a very difficult set of confounding variables. Informed consent issues are thorny, as are conflict of interest issues involving investigators. Although some of the panel thought that best medical treatment should include only approved drug and device combinations, it was noted that the use of heparin is not approved or been proven effective for treatment of acute stroke. They thought the potential confounding variables should be addressed during the trial design. Dr. Canady summarized by stating that the panel had given FDA "much latitude" for case-by-case consideration.

5) When should evaluation of these outcome measures be made? When should primary and secondary effectiveness be measured? What length of follow-up is appropriate to establish the safety of these therapies?

The panel recommended that primary effectiveness be measured immediately by radiographic means and within 24 hours clinically for acute studies. The three-month outcome measurement is somewhat arbitrary and could be closer to the clinical event, with status at 24 hours being a good predictor. Strong consideration should be given to early assessment, and the influence of rehabilitation on speed and completeness of recovery should be noted.

Longer follow-up to see long-term benefits was recommended. Study success can be evaluated at two years for restenosis rates and for evaluation of prevention and effectiveness. Using Kaplan Meier techniques two-to-three-year results can project five year rates if the numbers are sufficient. Statistical questions should be based on sample sizes sufficient to show equivalency.

On length of follow-up assessment for safety, it was noted that it may also be important to evaluate safety of stent use in the hands of less experienced providers.

FDA PRESENTATION ON NEUROLOGICAL PROTECTIVE COOLING

Janine Morris of the FDA began the session on device modalities to induce hypothermia for neuroprotection for the indications of cardiac arrest, traumatic head injury, stroke, and aneurysm surgery. She summarized the history of therapeutic hypothermia and listed technologies to provide hypothermia, such as cooling blankets, endovascular cooling catheters, and cardio-pulmonary bypass. Ms. Morris read three FDA questions regarding general safety issues, temperature monitoring, and study design for the four specific patient populations listed above. In conclusion, she noted that although the FDA believes the clinical benefit of hypothermia needs to be assessed for these patients, the agency recognizes that hypothermia may already be part of the intraoperative

management of patients with intracranial aneurysms who are undergoing surgery. She stated that the FDA hopes these questions will provoke productive discussion of hypothermia study endpoints and controls. .

OPEN PUBLIC HEARING

Christopher M. Loftus, M.D., F.A.C.S., from the University of Oklahoma College of Medicine, discussed clinical trials of cooling devices for neurological protection. He noted that hypothermia can be deep or mild and summarized data on both to date. He listed the four patient groups for whom it might be useful and noted that hypothermia is being used empirically, although there is no level 1 evidence of its efficacy. The Iowa Practice Survey of 1996 provided some data on hypothermia in aneurysm surgery, finding potential risks of cardiac arrhythmias, coronary ischemia, infection, and aggravation of cold-related diseases. There are also data on use of mild hypothermia for head injury based on a randomized trial of 82 patients. Dr. Loftus explained methods of delivery and noted that clinical randomized trials are being done on surface, endovascular, and other means of cooling.

Dr. Loftus explained the trial design and current status of a trial on intraoperative hypothermia for aneurysm surgery. He outlined patient eligibility criteria, basic protocol, and assessment time frames, and methods. The prospective pilot trial found no statistical differences, but there was some indication of benefit in using hypothermia for treatment of subarachnoid hemorrhage. He stressed that because the technology is evolving, adherence to target temperature protocol is important.

Michael DeGeorgia, M.D., of the Cleveland Clinic Foundation, reviewed the statistics on stroke and the findings of the PROACT II study on severe strokes. He noted

the need for a new approach for patients with severe stroke and cited a study at the University of Texas that showed hypothermia produced significantly lower infarct volume and less damage. He described the protocol for a pilot study at the Cleveland Clinic on Cooling for Acute Ischemic Brain Damage (which he referred to as COOL AID) and explained the inclusion criteria and surface cooling protocol.

Derk Krieger, M.D., Ph.D., also of the Cleveland Clinic Foundation,

explained the baseline characteristics of the Cleveland study and referred the audience to published findings on feasibility and safety findings, as well as clinical outcome and radiological outcome data. He stated that study results suggest that moderate hypothermia induced by surface cooling is feasible in patients with acute stroke undergoing thrombolytic therapy. Dr. Krieger listed patient selection, time window, temperature depth and duration, and clinical endpoints or surrogate markers as important considerations for future clinical trials.

INDUSTRY PRESENTATIONS

Christopher Ogilvy, M.D., of Harvard Medical School, spoke on behalf of **Innercool Therapies,** saying that efficacy of mild hypothermia in neurosurgery is well proven in animal models and is more effective than any drug regimen to date. He discussed methods and problems of hypothermia produced through the skin and listed advantages and disadvantages of endovascular approaches to hypothermia via an endovascular temperature control catheter. He explained the functioning of the device and its clinical application and listed possible efficacy outcomes as ability to reach desired temperature in desired time, ability to maintain desired temperature, and ability to safely rewarm patient. Safety concerns include vascular injury, liver function, and cardiac

function. He listed considerations for endovascular hypothermia in other applications as well.

Michael Diring, M.D., of the Washington University School of Medicine, spoke on behalf of **Alsus Corporation.** He stated that the goal of neuroprotection is reduction of primary injury and prevention of secondary injury and controlling intracranial pressure by limiting edema. He asked if potential target populations could be expanded by using hypothermia without intubation. He recommended randomized controlled trials with identical management of control group except for the application of hypothermia and suggested clinical questions for each potential patient group. For ischemic stroke, he asked whether hypothermia could be used for moderate stroke and could be achieved fast enough. For head injury, he wondered whether entry criteria can be broadened to include less severe patients. For cardiac arrest, variables include the interval to institution of CPR, duration of asystole, and duration of cooling. For subarachnoid hemorrhage, hypothermia is being studied intraoperatively for aneurysm repair and could be used to reduce injury from vasospasm if selection criteria and timing are worked out.

Dr. Diring suggested dichotomous primary endpoints, depending on the population. If the population is severely injured, the primary endpoint could be independence/dependency; if less severe patients are studied, then it could be degree of disability. He listed factors involved in temperature monitoring, noting that core (bladder) temperature can be monitored easily and safely. Questions to be answered include safety of temperatures below 32 degrees and effectiveness of temperatures over 34 degrees. Dr. Diring noted that optimal duration of hypothermia depends on the disease and treatment goal and it may be limited by complications. The rate of cooling and rewarming are

important; rapid cooling using internal devices may enhance neuroprotective effects, but too rapid rewarming can produce rebound ICP. He concluded that medical management should include standardization of other interventions, strict control of medical management, and minimization of management differences between groups.

OPEN PANEL DISCUSSION

James C. Grotta, M.D., Consultant on FDA's Peripheral and Central Nervous System Drugs Advisory Committee, as the lead panel reviewer for this topic, addressed the panel. He listed possible indications of neurological protective cooling such as global ischemia, focal ischemia, head trauma, intra-operative cooling, and other, and discussed mechanisms of hypothermia. Preclinical studies have indicated that there is a brief time window of effectiveness during which hypothermia treatment must begin for it to be effective. Hypothermia during reperfusion increases the amount of neuroprotection. Phases and goals include induction of hypothermia, maintenance of hypothermia, and rewarming after hypothermia. The induction phase seeks to reach target temperature rapidly by various methods. The maintenance phase seeks to maintain temperature at a therapeutic level, via drugs to induce paralysis to prevent shivering, and to avoid complications of cold-related injuries. During rewarming, the patient must return to stable temperature gradually.

Dr. Grotta then described a safety and feasibility trial on moderate induced hypothermia for cardiac arrest conducted at the University of Texas. He explained the trial design, hypothermia protocol, and rewarming procedures. Of the nine subjects, four survived and five died, with three completely returned to baseline functioning. Dr. Grotta also noted that of 156 cardiac arrest patients in the study period, only six qualified for the

study. Dr. Grotta noted limitations on the data, including that it was not a randomized or blinded trial, hypothermia was not achieved quickly, and rewarming was not well controlled. Dr. Grotta recommended a better method for achieving and maintaining hypothermia and rewarming, randomization, waiver of consent for future trials, including in-hospital arrests and myocardial infarction patients, maintaining 33 degrees for 24 hours, measuring survival and cognition at one month, and control of secondary outcomes such as infection, arrhythmias, etc.

Dr. Grotta also reviewed a published 1998 study by Schwab et al. on moderate hypothermia for severe stroke and a study by Kammersgaard on modest hypothermia in focal stroke. He concluded from these studies that future stroke trials must achieve hypothermia quickly and be maintained through reperfusion. Mild hypothermia may be practical, with 33-35 degrees a reasonable target range. Moderate hypothermia for delayed edema in malignant middle cerebral artery is one possibility. Survival and disability should be studied at three months.

Dr. Grotta reviewed the NABIS:H multicenter trial to determine if surface-induced moderate hypothermia begun within six hours of injury and maintained for 48 hours improves outcome without toxicity. He outlined enrollment criteria and patient management and reviewed outcome and mortality, which were nearly identical for both groups although the study showed a trend toward better outcome for patients who were hypothermic to begin with. He recommended that future research examine whether moderate hypothermia is a more effective treatment for those who are already hypothermic.

Dr. Grotta also described a 1999 abstract by Hindman et al. on hypothermia during aneurysm surgery that showed patients with SAH showed a nonsignificant trend toward less neurological deterioration and a better long-term outcome.

Dr. Grotta concluded that hypothermia consistently and potently reduces damage after experimental cerebral ischemia and trauma. He urged that hypothermia must be achieved fast and should be maintained through the reperfusion phase. A reasonable range is 33 to 35 degrees, and mild hypothermia may be practical. Dr. Grotta stated that clinical trials have been encouraging in that they have shown safety and signals of efficacy, but existing techniques for achieving and maintaining hypothermia are unsatisfactory and new approaches are needed.

Panel Deliberations

1) What are the safety parameters that would be important to measure in any study population? Are there safety questions that are unique to a specific technology?

The panel recommended that temperature remain in the 32-24 degree range with duration of hypothermia of less than 24 hours, although this depends on the indication. The rate of cooling should be fast and rate of rewarming should be controlled. Rewarming should be one degree every four to six hours and cooling as fast as possible regardless of indication.

Dr. Witten asked if cooling should be allowed to last longer than 24 hours. The panel noted problems with indwelling catheters, infection, pneumonia, and other complications of immobility.

2) What temperature monitoring methods and anatomic sites do you recommend?

The panel recommended bladder temperature and pulmonary temperature. Brain temperature was acknowledged to be a different issue. Hats similar to those used to prevent hypoxic brain cooling for neonates were mentioned as a possibility.

3) What are your suggestions on clinical study design for evaluation of hypothermic devices for the following patient groups: those with cardiac arrest, head trauma, stroke, and aneurysm surgery?

Cardiac Arrest Patients

What are important inclusion/exclusion criteria?

The panel stated that two ongoing large trials in Europe and the Pacific will produce much information these patient subgroups. They therefore recommended excluding as few patients as possible to see responsiveness. Unless there is a well documented reason to exclude a category, patients should be included.

What are important safety parameters?

The panel urged keeping the patients as cool as possible. There was disagreement within the panel on exclusion of patients with Raynaud's and most cold-related diseases for safety reasons, although status epilepticus in some patients may be a safety parameter. The panel noted that a deferred or waived consent is a difficult but important consideration.

What considerations are involved in identifying appropriate outcome measures and when should they be measured?

The panel agreed that left ventricular function should be followed because data stratification may be necessary later. Basic outcome measures become evident quickly for those who survive and can be measured within a week or a month. Cognitive evaluation

should be done at one month with neuropsychological testing and repeated at six months and perhaps even farther out.

What characteristics should be considered in defining the appropriate control population?

The panel suggested a comparison of cooled and not cooled patients. It was noted that the cardiac arrest landscape is changing with atrial defibrillators, and a control group is crucial.

Traumatic Head Injuries

What are important inclusion/exclusion criteria?

The panel agreed that randomization after waiver of informed consent is advisable. There should be a cohort group of alcohol/drug trauma patients.

What safety parameters are important to measure?

The panel had no additional recommendations.

What considerations should be taken into account when identifying appropriate outcome measures and when should these be made?

The panel noted that outcome for head trauma patients cannot be assessed as quickly as for patients with cardiac arrest and that they should be measured at six months. The panel agreed that it was premature to set specific evaluation schedules. There was discussion on whether patients with poor initial neuropsychiatry testing should be denied hypothermic treatment to save life. It was noted that as with cardiac arrest patients, it is relevant to know if the patients survive intact or with severe impairment.

What characteristics should be considered in defining control population?

The panel's only additional recommendation was that in the control population the severity of trauma in relation to the rest of the body should be noted because this may affect outcome.

Are there special considerations for treating pediatric patients?

The panel thought that considerations were not different for the pediatric group. They stressed inclusion of pediatric patients because head trauma is an important pediatric public health problem, and the outcomes are better for younger patients, both those with head injuries and in response to hypothermia.

Stroke

In general, the panel agreed with the earlier lead panel discussant presentations. They recommended not sedating and paralyzing awake patients but lowering their temperatures to 35 degrees in combination with other treatments as a therapeutic modality. Combination treatments were not viewed as a problem, even when combining hypothermia and thrombolytic treatments.

What are important inclusion/exclusion criteria?

It was recommended that a study should be dichotomized between moderate hypothermia to 35 degrees for awake patients and deeper cooling for others. Proximal carotid occlusions should be included and interventional measures should be explicit. One experimental intervention at a time should be done if possible, but hypothermia can be combined with others if the variables can be controlled. Hypothermia can also be used on patients eligible to get intravenous tPA.

What safety parameters should be measured?

In general, hypothermia patients should be monitored by CT scans. For patients with large focal stroke there is no alternative to intracranial monitoring devices.

What considerations should be taken into account when identifying appropriate outcome measures and when should they be made?

Outcome should be measured at three to six months. Functional scales should be used to ensure primary and secondary effectiveness outcomes.

What characteristics should be considered in defining the appropriate control?

The panel agreed that control populations are desirable, although it was noted that there is no control for stroke patients with medical treatment only. In defining the control, it should be noted that patients receiving hypothermia are on Demerol.

Aneurysm Surgery

What are important inclusion/exclusion criteria?

Obese patients should be excluded from external cooling because of practical difficulties but not from internal cooling. Those who bleed during the surgery should be a targeted group.

What safety parameters should be measured?

Safety parameters that should be monitored are left ventricular changes related to ischemia. Subarachnoid hemorrhage patients on blockers should be monitored and not subjected to prolonged hypothermia. It was noted that in vasospasm other treatment, such as angioplasty could be confounding.

What considerations should be taken into account when identifying outcome measures and when should they be made?

The panel stressed the importance of cognitive measures. Glasgow scales should be used, and neurological deterioration in the hospital from vasospasm should be measured. Patients with unruptured aneurysms should be studied to see why they are not improving and how their results can be improved, but they should not be excluded. Intracerebral hemorrhage is an orphan indication that should be added.

What characteristics should be considered in defining the appropriate control?

Dr. Witten asked the panel for more recommendations on control groups, specifically whether comparisons would be made for aneurysm to aneurysm, based on location, or on cooling to no cooling, or for degrees of cooling. Rather than using regular control groups, the panel suggested cooling all aneurysm patients and looking for a dose response on what temperature is best.

Dr. Diring of the Washington University School of Medicine then asked to address the panel. He said there seemed to be confusion over the effect of treatment and effect of the device. He urged a separation of issues into how a device accomplishes hypothermia and the clinical efficaciousness of that cooling. For clinical studies, first sponsors must show if the hypothermia hypothesis works and if it is an effective treatment, then show the device works.

On behalf of the FDA, **Dr. Witten** thanked the panel and participants.

Panel Chair Dr. Canady thanked the panel and all presenters and adjourned the day's session at 5:05 p.m.

I certify that I attended the Open Session of the Neurological Devices Advisory Panel Meeting on November 16, 2000, and that this summary accurately reflects what transpired.

Janet L. Scudiero, M.S.
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Alexa I. Canady, M.D.
Panel Chairperson

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