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COX-2 Inhibitors: A Role in Alzheimer's Disease?

The Technology

Celecoxib (Celebrex®) and rofecoxib (Vioxx®) are the first of a new class of nonsteroidal anti-inflammatory drugs (NSAIDS) called COX-2 inhibitors. As anti-inflammatory agents they are approved for such disorders as osteoarthritis. The long term adverse effects of older NSAIDs have been one of the primary reasons for the emergence and testing of COX-2 inhibitors as a possible alternative to regular NSAIDs. They may cause less gastrointestinal events, such as ulcers, than traditional NSAIDs. Currently only surrogate outcomes, such as endoscopic evidence of ulcers, have been demonstrated to be reduced. Evidence of clinical reduction in symptomatic ulcers and gastrointestinal bleeds are still lacking.

This class of compounds is also being evaluated in other disorders including the treatment or prevention of Alzheimer's disease (AD).

Regulatory Status

Celecoxib is approved in Canada for acute and chronic use in the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults. Another COX-2 inhibitor, rofecoxib (Vioxx®), has just received a Notice of Compliance from Health Canada. Rofecoxib is indicated for the acute and chronic treatment of osteoarthritis, relief of pain in adults and treatment of primary dysmenorrhea.[a]

Patient Group

"AD is defined as a neurodegenerative disease characterized by loss of intellectual abilities, increased propensity to emotional disabilities, and gradual decline of personality." [1] Two types of brain lesions, the neurofibrillary tangle and the beta amyloid plaque, characterize AD pathology.[2] The prevalence of AD in Canada is 5.1% of all people aged 65 and over. The age-standardised rate increases from 2.4% among those aged 65-74, to 34.5% among those aged 84 and over. The female:male ratio is 2.1 overall, but is 2.9 in the oldest group.[3] AD accounts for almost two-thirds of all cases of dementia in Canada.[3] The majority of the remaining dementia cases are referred to as Vascular dementia (VaD).[4] VaD and AD frequently coexist - a condition called mixed dementia.[4]

Current Treatments

There are a number of agents that have been tested and found to be effective in the symptomatic treatment of AD, although the level of improvement is modest.[b] There are no therapies that have been definitively proven to prevent or reduce the probability of developing Alzheimer's disease or to slow the progression of the disease.

[a] A CCOHTA economic evaluation will be published early next year evaluating the cost-effectiveness of COX-2 inhibitors in the treatment of osteoarthritis.
[b] See upcoming CCOHTA report "Treatment of Alzheimer's Disease: A comparative Analysis"

Potential Cost/Rate of Diffusion

A recent economic evaluation determined that the annual cost per Alzheimer's disease patient in Canada ranged from $9,451 for mild disease to $36,794 for severe disease.[5] The major cost drivers result from institutionalization (approximately 50% of all Alzheimer patients are in nursing homes) and unpaid direct care and supervision costs. Based on a conservative cost-of-illness study, the net economic cost of dementia in Canada was estimated to be $3.9 billion in 1991.[6] Adding some indirect costs could bring that figure to over $5 billion.[5] Due to the ageing of the Canadian population, the number of patients with AD will increase more than threefold from 1991 to 2031 if there are no effective preventative measures found. Based on 1998 estimated population statistics, over 3.7 million Canadians may be eligible for preventative therapy. By 2010 over 4.8 million Canadians will be over 65[7] and could qualify for therapy. Although a number of risk factors for the development of AD are known, (e.g. increasing age and family history) the optimal timing of preventative measures are unknown.

Concurrent Developments

There is a great deal of research activity surrounding the possible benefit of NSAIDs and, in particular, COX-2 inhibitors. Much of the work, to date, has been in animals and in vitro studies to determine associations and mechanisms of action. A two-year double-blind, placebo controlled trial is evaluating whether ibuprofen is efficacious in delaying the progression of cognitive symptoms in people with age-related cognitive losses who are at risk for developing AD.[8] Another study is evaluating rofecoxib in a double-blind, placebo controlled trial to determine whether a COX-2 inhibitor will prevent the development of AD.[9]

Other anti-inflammatory drugs are also being evaluated. These include prednisone, colchicine, and hydroxychoroquine.[10-12] A number of drugs that impact non-inflammatory mechanisms are also being evaluated. For example, there are three multicenter, prospective randomized controlled trials evaluating the effect of estrogen replacement therapy.[2] Vitamin E and donepezil are being assessed to determine their potential to prevent AD.[13]

There are some other potential preventative measures that may be of benefit. Since a large number of dementia cases are either due to cerebrovascular disease or have a cerebrovascular component there is scientifically plausible hope that treatment with antihypertensives, HMG coenzyme A reductase inhibitors, and/or anticoagulants may reduce the incidence of dementia.[4] However, proof of this effect is also lacking.

Assessing the Evidence

A. NSAIDs

Several lines of evidence indicate that AD may involve a chronic inflammatory process.[1, 14, 15] The most compelling clinical evidence is the large number of epidemiological studies demonstrating that anti-inflammatory drugs, particularly NSAIDs, delay or attenuate the clinical expression of AD[16-19] or reduce the rate of decline.[18] These studies have been conducted in various countries with drugs ranging from NSAIDs to steroids to dapsone, and in patients with or without arthritis, utilizing case control and population based epidemiological techniques.[19]

A review of 17 epidemiological studies concluded that NSAID use might have a protective effect against AD.[19] Risk reduction ranged from 35 to 50%. Since then several more epidemiological studies have been published generally confirming this conclusion.[16, 20] However, some studies have failed to find a significant effect.[21-24] One of the primary difficulties in assessing efficacy or effectiveness from treatment or prevention is the lack of definitive diagnostic criteria for AD, especially for incident cases. Clinical criteria for the diagnosis of AD are highly sensitive but also result in high false positive rates.[25]

There are several questions, as well as criticisms, that have arisen as a result of the epidemiological studies:

- recall bias in interview type studies, especially when dealing with a disease such as AD

- use of proxy respondents (usually close relatives) which has not been found to be very reliable[26]
- nonprescription NSAID utilization was frequently not addressed
- lack of control for confounding by indication
- studies employing prevalent cases may have survival bias (those using NSAIDs could have died earlier than non-users)
- lack of diagnostic specificity, especially on detecting incident cases
- longitudinal studies frequently did not monitor ongoing use

The studies demonstrating no beneficial effects can also be criticized. For example the negative study by in't Veld[22] was probably too underpowered to detect an association.[27] The study by Beard et al. may suffer from selection bias (presence or absence of a disease might affect the odds ratio).[21] Also the definition of exposure to NSAIDs may have masked benefit in this latter study.

One RCT using indomethacin demonstrated a significant positive impact on the rate of decline of a number of cognitive measures.[28] However, the study was underpowered (44 subjects) and had a high dropout rate (16/44) in the indomethacin group.[29] One short term RCT (7 days) demonstrated improvement in short term memory in healthy elderly volunteers.[30]

Although the potential mechanism for NSAIDs has not been elucidated, it may involve the suppression of microglial activity rather than impacting the formation of senile plaques or neurofibrillary tangles.[31] Activated microglia are found within or near all AD lesions.[2] Although there has been laboratory evidence of inflammation, a suitable animal model has not been developed that truly mimics AD. This has stymied investigation into possible mechanisms and treatment or preventative strategies. Recent laboratory evidence points to possible COX-2 mediated mechanisms (see below).

B. COX-2 inhibitors

Currently there are no clinical trials that have evaluated COX-2 inhibitors for the treatment or prevention of AD, although results are expected soon. Most of the evidence comes from in vitro and animal work. There is a substantial amount of COX-2 in neurons of the neocortex and hippocampus in normal brains.[29] COX-2, but not COX-1, production may be stimulated in AD.[29] Studies using cell cultures and animal models suggest that COX-2 may contribute to neurodegeneration through apoptosis mechanisms.[10,11,32] COX-2 has been preferentially localized in neurofibrillary tangle positive neurons with damaged axons. Therefore COX-2 inhibitors might affect neuronal activities independent of glial/inflammatory activity.[10]

Implementation Issues

Several obstacles have stood in the way of obtaining definitive proof of benefit from NSAIDs:

- a lack of a comprehensive list of risk factors for AD to assess protective effect
- the requirement for large size trials that may require many years to conduct to detect a decrease in the probability of developing AD
- a lack of agreement on suitable outcome endpoints
- no clear data to indicate the optimal timing of therapy[29]

The long term adverse effects of NSAIDs have been one of the primary reasons for the emergence and testing of COX-2 inhibitors as a possible alternative to regular NSAIDs. Currently only animal and in vitro evidence exists. Clinical trials are required as well as long term experience with these drugs to assess their safety record.

The studies that are currently evaluating both COX-2 selective agents as well as regular, non-selective NSAIDs should provide evidence of benefit, if any, in protection against AD and/or impact on the rate of cognitive decline in existing AD patients. A critical risk/benefit ratio should be conducted to determine the clinical utility of NSAIDs.[14] It may be possible to compare and contrast the various agents, provided similar outcomes are measured and full monitoring of both beneficial and adverse events is recorded. At the same time, other agents being evaluated should be compared to these drugs to determine optimal

therapy. Even if some agents are identified that may be of benefit in preventing AD, the optimal time of when to initiate therapy will still be elusive. Some important questions remain to be answered:

- how many years in advance must therapy be given to have a protective effect?
- will increasing the years prior to the onset improve benefit?
- will lower doses have the same beneficial effect?
- will these drugs delay onset of Alzheimer's disease or prevent cases from occurring?
- will these drugs be useful for both prevention and treatment?
- what benefit might accrue by combining various therapeutic strategies?

Finally, although COX-2 inhibitors appear to be equally efficacious anti-inflammatory agents in comparison to traditional NSAIDs:

- proof from randomized and/or well designed phase IV trials on their improved side effect profile needs to be published and
- these drugs are unlikely to confer benefit for the prevention of cardiovascular/ cerebrovascular events since they lack anti-platelet effects. This could be an especially important issue considering the age of the population that may benefit from preventative therapy

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References

1. Popovic M, Caballero-Bleda M, Puelles L, et al. Importance of immunological and inflammatory processes in the pathogenesis and therapy of Alzheimer's disease. **Intern J Neuroscience** 1998;95(3-4):203-236.
2. Brinton RD, Yamazaki RS. Advances and challenges in the prevention and treatment of Alzheimer's disease. **Pharm Res** 1998; 5(3):386-398.
3. Canadian study of health and aging: study methods and prevalence of dementia. Canadian Study of Health and Aging Working Group. **CMAJ** 1994;150(6):899-913.
4. Patterson CJ, Gauthier S, Bergman H, et al. The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. **CMAJ** 1999;160(12 Suppl):S1-15.
5. Hux MJ, O'Brien BJ, Iskedjian M, et al. Relation between severity of Alzheimer's disease and costs of caring. **CMAJ** 1998;159(5):457-465.
6. Ostbye T, Crosse E. Net economic costs of dementia in Canada. **CMAJ** 1994;151(10):1457-1464.
7. United States Census Bureau. International Data Base. IDB Summary Demographic Data. **Canada demographic indicators: 1998 and 2010. Midyear population, by age and sex: 1998 and 2010 (population in thousands).** [1 screen]. Available from: URL: http://www.census.gov/cgi-bin/ipc/idbsum [accessed 1999 Nov 16]
8. Small GW. **Anti-inflammatory treatment for age-associated memory impairment : a double-blind placebo-controlled trial** [protocol]. Alzheimer's Disease Education & Referral Center. Clinical Trials Database. Available from: URL: http://www.alzheimers.org/trials/basicsearch.html [accessed 1999 Oct 8]
9. Rickey T. **Physicians study whether "super-aspirin" prevents Alzheimer's** [press release] 1999 Nov 19. [2 screens]. Available from: URL: http://www.rochester.edu/pr/releases/med/cox2.htm [accessed 1999 Jun 9]

10. Pasinetti GM. Cyclooxygenase and inflammation in Alzheimer's disease: experimental approaches and clinical interventions. **J Neurosci Res** 1998;54(1):1-6.
11. Aisen PS, Pasinetti GM. Glucocorticoids in Alzheimer's disease. The story so far. **Drugs Aging** 1998;12(1):1-6.
12. Hendrie HC. Epidemiology of dementia and Alzheimer's disease. **Am J Geriatr Psychiatry** 1998;6(2 Suppl 1):S3-18.
13. National Institute on Aging. NIA News: Alzheimer's Disease Research Update. **NIA launches national study to treat mild cognitive impairement - March 15, 1999.** [8 screens]. Available from: URL: http://www.alzheimers.org.nianews/nianews19.html [accessed 1999 Oct 26]
14. Flynn BL, Theesen KA. Pharmacologic management of Alzheimer disease part III: nonsteroidal antiinflammatory drugs - - emerging protective evidence? **Ann Pharmacother** 1999;33(7-8):840-849.
15. O'Banion MK. Cyclooxygenase-2: molecular biology, pharmacology, and neurobiology. **Crit Rev Neurobiol** 1999;13(1):45-82.
16. Rozzini R, Ferrucci L, Losonczy K et al. Protective effect of chronic NSAID use on cognitive decline in older persons. **J Am Geriatr Soc** 1996;44(9):1025-1029.
17. Breitner JC, Welsh KA, Helms MJ, et al. Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs. **Neurobiol Aging** 1995;16(4):523-530.
18. Rich JB, Rasmusson DX, Folstein MF, et al. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. **Neurology** 1995;45(1):51-55.
19. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. **Neurology** 1996; 47(2):425-432.
20. Stewart WF, Kawas C, Corrada M, et al. Risk of Alzheimer's disease and duration of NSAID use. **Neurology** 1997; 48(3): 626-632.
21. Beard CM, Waring SC, O'Brien PC, et al. Nonsteroidal anti-inflammatory drug use and Alzheimer's disease: a case-control study in Rochester, Minnesota, 1980 through 1984. **Mayo Clin Proc** 1998;73(10):951-955.
22. in 't Veld BA, Launer LJ, Hoes AW, et al. NSAIDs and incident Alzheimer's disease. The Rotterdam study. **Neurobiol Aging** 1998;19(6):607-11.
23. May FE, Moore MT, Stewart RB, et al. Lack of association of nonsteroidal anti-inflammatory drug use and cognitive decline in the elderly. **Gerontology** 1992;38(5):275-279.
24. Henderson AS, Jorm AF, Christensen H, et al. Aspirin, anti-inflammatory drugs and risk of dementia. **Int J Geriatr Psychiatry** 1997;12(9):926-30.
25. Mayeux R, Saunders AM, Shea S, et al. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. **N Engl J Med** 1998;338(8):506-11.
26. Breitner JC. Exposure classification: the bugbear of dementia epidemiology. **Neurobiol Aging** 1998;19(6):613-614.
27. Mortimer JA. New findings consistent with Alzheimer's-NSAIDs link. **Neurobiol Aging** 1998;19(6):615-616
28. Rogers J, Kirby LC, Hempelman SR, et al. Clinical trial of indomethacin in Alzheimer's disease. **Neurology** 1993;43(8):1609-1611.
29. Aisen PS, Davis KL. Anti-inflammatory therapy for Alzheimer's disease: a status report. **Int J Geriatr Psychopharmacol** 1997;1(1):2-5.
30. Bruce-Jones PN, Crome P, Kalra L. Indomethacin and cognitive function in healthy elderly volunteers. **Br J Clin Pharmacol** 1994;38(1):45-51.
31. Mackenzie IR, Munoz DG. Nonsteroidal anti-inflammatory drug use and Alzheimer-type pathology in aging. **Neurology** 1998; 50(4):986-990.
32. Dubois RN, Abramson SB, Crofford L, et al. Cyclooxygenase in biology and disease. **FASEB J** 1998;12(12):1063-1073.
33. Freedman AN, Michalek AM, Weiss HA, et al. Aspirin use and p53 expression in colorectal cancer. Cancer Detect Prev 1998;22(3):213-218.
34. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. Cancer Res 1988;48(15):4399-4404.

35. Muscat JE, Stellman SD, Wynder EL. Nonsteroidal antiinflammatory drugs and colorectal cancer. Cancer 1994;74(7):1847-1854.
36. Logan RF, Little J, Hawtin PG, et al. Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: case-control study of subjects participating in the Nottingham faecal occult blood screening programme. BMJ 1993;307(6899):285-289.
37. La Vecchia C, Negri E, Franceschi S, et al. Aspirin and colorectal cancer. Br J Cancer 1997;76(5):675-677.
38. Rosenberg L, Louik C, Shapiro S. Nonsteroidal antiinflammatory drug use and reduced risk of large bowel carcinoma. Cancer 1998; 82(12):2326-2333.
39. Smalley W, Ray WA, Daugherty J, et al. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. Arch Intern Med 1999;159(2):161-166.
40. Bucher C, Jordan P, Nickeleit V, et al. Relative risk of malignant tumors in analgesic abusers: effects of long-term intake of aspirin. Clin Nephrol 1999;51(2):67-72.
41. Friedman GD, Coates AO, Potter JD, et al. Drugs and colon cancer. Pharmacoepidemiol Drug Saf 1998;7(2):99-106.
42. Paganini-Hill A, Chao A, Ross RK, et al. Aspirin use and chronic diseases: a cohort study of the elderly. BMJ 1989;299(6710):1247-1250.
43. Thun MJ, Namboodiri MM, Heath CW. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 1991;325(23):1593-1596.
44. Greenberg ER, Baron JA, Freeman DH, et al. Reduced risk of large-bowel adenomas among aspirin users. Polyp Prevention Study Group. J Natl Cancer Inst 1993;85(11):912-916.
45. Giovannucci E, Rimm EB, Stampfer MJ, et al. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. Ann Intern Med 1994;121(4):241-246.
46. Sheng H, Shao J, Kirkland SC, et al. Inhibition of human colon cancer cell growth by selective inhibition of cyclooxygenase-2. J Clin Invest 1997; 99(9):2254-2259.
47. Hara A, Yoshimi N, Niwa M, et al. Apoptosis induced by NS-398, a selective cyclooxygenase-2 inhibitor, in human colorectal cancer cell lines. Jpn J Cancer Res 1997;88(6):600-604.
48. Sawaoka H, Kawano S, Tsuji S, et al. Cyclooxygenase-2 inhibitors suppress the growth of gastric cancer xenografts via induction of apoptosis in nude mice. Am J Physiol 1998;274(6 Pt 1):G1061-G1067.
49. Gustafson-Svärd C, Lilja I, Hallböök O, et al. Cyclo-oxygenase and colon cancer: clues to the aspirin effect? Ann Med 1997;29(3):247-252.
50. Reddy BS, Rao CV, Seibert K. Evaluation of Clyclooxygenase-2 inhibitor for potential chemopreventive properties in colon carcinogenesis. Cancer Res 1996;56(20):4566-4569.
51. Sheehan KM, Sheahan K, O'Donoghue DP, et al. The relationship between cyclooxygenase-2 expression and colorectal cancer. JAMA 1999;282(13):1254-1257
52. Kreidié A. COX-2 drug effective in treating colon polyps. Medical Post 1999;35(37):1,45
53. Dubois RN, Abramson SB, Crofford L, et al. Cyclooxygenase in biology and disease. FASEB J 1998;12(12):1063-1073.
54. Vainio H, Morgan G, Kleihues P. An international evaluation of the cancer-preventive potential of nonsteroidal anti-inflammatory drugs. Cancer Epidemiol Biomarkers Prev 1997;6(9):749-753.
55. Singh AK, Trotman BW. Use and safety of aspirin in the chemoprevention of colorectal cancer. J Assoc Acad Minor Phys 1998;9(2): 40-44.
56. Spagnesi MT, Tonelli F, Dolara P, et al. Rectal proliferation and polyp occurrence in patients with familial adenomatous polyposis after sulindac treatment. Gastroenterology 1994;106 (2):362-366.
57. McAdam BF, Catella-Lawson F, Mardini IA, et al. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci U S A 1999; 96(1): 272-277

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