Are Preferences for Cyclooxygenase-2 Inhibitors Influenced by the Certainty Effect?

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ABSTRACT. ***Objective.*** To test whether the widespread use of cyclooxygenase-2 (COX-2) inhibitors may be mediated in part by the certainty effect, i.e., by a perception that COX-2 inhibitors eliminate the risk of serious gastrointestinal (GI) events in contrast to merely reduce their risk.

Methods. Patients' preferences for conventional nonsteroidal antiinflammatory drugs (NSAID) and COX-2 inhibitors for treatment of arthritis were predicted across a range of absolute risks of GI events using an Adaptive Conjoint Analysis survey.

Results. Preferences for COX-2 inhibitors were much stronger when the risk of serious GI events was eliminated in contrast to reduced, even though the absolute risk reduction (ARR) was the same. Few patients (22%) preferred COX-2 inhibitors when the risk associated with NSAID and COX-2 inhibitors was 4% and 2%, respectively (ARR = 2%). In contrast, the majority (90%) preferred COX-2 inhibitors when the risk associated with NSAID and COX-2 inhibitors was 2% and 0%, respectively (ARR = 2%). We obtained similar findings regardless of the ARR.

Conclusion. The willingness shown by older adults to pay for COX-2 inhibitors may reflect a misperception of the risk of toxicity associated with these medications. (J Rheumatol 2004; 31:591–3)

Key Indexing Terms:
ARTHRITIS NONSTEROIDAL ANTIINFLAMMATORY DRUGS CONJOINT ANALYSIS
CYCLOOXYGENASE-2 INHIBITORS TREATMENT PREFERENCES

The availability of cyclooxygenase-2 (COX-2) inhibitors is considered a major advancement for patients with arthritis and other painful conditions. Controlled trials have shown that these drugs cause fewer serious gastrointestinal (GI) events than nonselective nonsteroidal antiinflammatory drugs (NSAID) of equal efficacy[1,2].

As a result of their superior safety profile, COX-2 inhibitors are currently among the most widely prescribed medications available. The unprecedented popularity of this class of drugs contrasts with previous research finding that arthritis patients are generally reluctant to accept the risk of adverse effects, including those associated with COX-2 inhibitors[3-6]. We hypothesized that the popularity of COX-2 inhibitors may be mediated in part by the certainty effect, i.e., by a perception that COX-2 inhibitors eliminate the risk of serious GI events as opposed to reduce the risk of GI toxicity.

The certainty effect refers to the observation that people consistently prefer to eliminate risk rather than reduce it, even when the risk is diminished by equal amounts in both cases[7]. For example, this effect predicts that a reduction in the risk of an adverse effect from 1% to zero will be valued more highly than a reduction in the risk of an adverse effect from 2% to 1%. This effect is extremely robust and occurs in evaluations of environmental, monetary, and health risks independent of respondents' level of education[8].

To test our hypothesis, we used Adaptive Conjoint Analysis (ACA, Sawtooth Software®) to examine the preferences of patients with osteoarthritis (OA) for nonselective NSAID and COX-2 inhibitors over a range of probabilities for serious GI events.

MATERIALS AND METHODS

Participants. Consecutive patients with radiographic knee OA, followed in 3 community rheumatology practices affiliated with Yale University, were contacted via telephone one week after having received a letter describing the study. Those having pain in one or both knees on most days of the month and not having rheumatoid arthritis, gout, pseudogout, or bilateral knee replacements were asked to complete a questionnaire examining patients' opinions about arthritis treatments. This protocol was approved by the Human Investigations Committee at our institution.

Data collection. All data were collected in face-to-face interviews by a research assistant. Patient characteristics were ascertained by self-report

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Dr. Fraenkel is supported in part by a Career Development Award from the Department of Veterans Affairs Health Services Research and Development Service, an Arthritis Investigator Award from the Arthritis Foundation, and grants from the Yale Pepper Center and Health Care Relationships Program. Dr. Fried is supported by a K02 AG20113 from the NIA.

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Submitted May 27, 2003; revision accepted August 26, 2003.

and the Western Ontario and McMaster Universities Osteoarthritis Index[9]. Preference data were collected using ACA (Version 4.1, Sawtooth Software, Sequim, WA, USA) with respondents entering their answers directly to a laptop computer. ACA is a reliable and well validated interactive program that computes individual patient values (utilities) for specific medication characteristics based on a series of ranking and rating questions[10-12]. The software program allows the researcher to derive preferences for a range of options (both real and hypothetical) by specifying a value for each treatment characteristic. For each simulation, the file of the respondent's utilities is read and a computation is made of each respondent's relative utility for each product. Because preferences are predicted based on trade-offs between specific medication characteristics and not the medications themselves, they are less influenced by product recognition or brand preference.

In this study, the options of interest were nonselective NSAID and COX-2 inhibitors. Both NSAID and COX-2 inhibitors were described as being prescription drugs, beginning to work within 1–2 hours, and being equally effective (50% of patients benefit). NSAID were described as being taken twice a day with a cost of $17.50/month and COX-2 inhibitors once a day with a cost of $70.00/month. Both nonselective NSAID and COX-2 inhibitors were described as being associated with a risk of nausea, diarrhea, and/or heartburn. COX-2 inhibitors were described as decreasing the risk of serious GI events (ulcer or bleed requiring admission to hospital for treatment) by 50% relative to NSAID[1,2,13].

All characteristics were written using lay terminology. Medication benefit was described in terms of improvement in both symptoms and function and all adverse effects were described in terms of severity and reversibility of symptoms, likelihood of occurrence, and sequelae[14].

In view of the literature documenting significant variability in both patients' ability to interpret probabilities and preference for the presentation of probabilistic information[15], we used qualitative and quantitative frequency formats to describe the likelihood of adverse effects. In addition, to improve understanding of the level of risk associated with rare events, we provided patients with familiar examples[16]. The ranges of probabilities of benefits and adverse effects were based on randomized controlled data and longterm followup studies[1,2,13,17-20].

ACA questionnaire. The use of ACA to examine patient treatment preferences has been explained in detail[21]. Briefly, respondents were first asked to rate the importance of the difference between the best and worst estimate of each characteristic on a 4-point scale. This set of questions allows ACA to construct initial utility estimates for each respondent. For example: If 2 medications were acceptable in all other ways, how important would this difference be? Twenty-five percent of patients benefit versus 100% of patients benefit. Choose a number from the scale 1: not important at all; 2: somewhat important; 3: very important; and 4: extremely important. Second, to refine respondents' utilities, respondents evaluated a series of paired comparisons. For example: Which would you prefer? Two percent risk of ulcer and 75% of patients benefit or no risk of ulcer and 25% of patients benefit? Respondents rated their preferences using a scale of 1 to 9, in which 1 represented strong preference for the first choice (2% risk, 75% of patients benefit), 5 represented no preference, and 9 represented strong preference for the second choice (0 risk, 25% of patients benefit).

Each question involved choosing from a pair in which one option is superior in one characteristic, and the opposing option is superior in the other. The program uses the information obtained from each paired comparison to update the estimates of each respondent's utilities and to select the next pair of options. Final utilities are generated using regression analysis[12].

Analyses. Preference data derived from ACA were imported into SAS computer files (SAS Software, version 6.12, SAS Institute, Cary, NC, USA) and merged with the patient characteristics data set. We ran simulations using ACA to estimate preferences for COX-2 inhibitors and nonselective NSAID. ACA calculates estimates of individual patient preferences based on the utilities derived from the conjoint questionnaire using least-squares regression analysis. All simulations were analyzed using the first-choice model, which assumes that respondents prefer the option with the highest utility. We report the proportion of patients preferring COX-2 inhibitors over nonselective NSAID as we varied the absolute risk of serious GI events, while other medication characteristics were held constant. We used t test and chi-square statistics for continuous and dichotomous variables, respectively, to examine the relationship between treatment preferences and patient characteristics.

RESULTS

One hundred older adults with symptomatic knee OA were interviewed (participation rate 84%). The mean ± SD age of our sample was 70 ± 7 years (range 59–90); 79% were female, 92% Caucasian, 41% were college graduates, and 32% reported having an annual household income ≥ $60,000. The mean ± SD duration of knee pain was 11 ± 9 years; mean ± SD knee pain score = 12 ± 4 (maximum = 20), and mean ± SD physical function score 42 ± 14 (maximum = 68). The majority of patients reported current or previous use of nonselective NSAID (85%) and COX-2 inhibitors (76%). Thirty-five percent reported previously having dyspepsia due to NSAID, 22% an ulcer, and 5% had been hospitalized for a GI bleed.

The data in Table 1 show that preferences for COX-2 inhibitors (for the same absolute risk reduction) are much stronger when risk is eliminated as opposed to reduced, regardless of the risk of GI events associated with nonselective NSAID. For example, for an absolute risk reduction of 2%, few patients (22%) preferred COX-2 inhibitors when the risks associated with NSAID and COX-2 inhibitors were 4% and 2%, respectively. In contrast, the majority (90%) preferred COX-2 inhibitors when the risks associated with NSAID and COX-2 inhibitors were 2% and 0%, respectively. The same pattern was found for NSAID-associated risks of 6% (absolute risk reduction of 3%) and 8% (absolute risk reduction of 4%). Preferences were not related to age, education, knee pain, or functional status (data not shown).

Table 1. Predicted preferences for NSAID versus COX-2 inhibitors. Results are expressed as percentages.

	Annual Risk of Serious GI Events	Preferring COX-2 Inhibitors	Annual Risk of Serious GI Events	Preferring COX-2 Inhibitors
NSAID	8		4	
COX-2 inhibitor	4		0	
		28		96
NSAID	6		3	
COX-2 inhibitor	3		0	
		25		95
NSAID	4		2	
COX-2 inhibitor	2		0	
		22		90

DISCUSSION

We found that patient preferences for COX-2 inhibitors are strongly influenced by the appeal of zero risk, consistent with the certainty effect. Given that the only proven advantage of COX-2 inhibitors over nonselective NSAID is a lower risk of serious GI events, these findings suggest that the popularity of COX-2 inhibitors may be mediated in part by a perception that these drugs eliminate, as opposed to reduce, the risk of toxicity.

The immense appeal of eliminating risk, in contrast to reducing it, has been repeatedly seen in both medical and nonmedical arenas. Loewenstein and colleagues recently proposed that the certainty effect is mediated through emotions[22]. Thus, eliminating risk (i.e., decreasing the likelihood from 1% to 0) completely eliminates anxiety or concern, whereas decreasing risk (i.e., decreasing the likelihood from 2% to 1%) has little effect on the emotional feelings associated with the specific risk in question.

Our results must be interpreted in view of the limitations of the study. First, despite our efforts to recruit patients from diverse practices, our study sample was homogenous, thereby limiting the generalizability of our results. The cost estimates assumed that participants would pay out-of-pocket for their medications. For patients having a prescription drug plan, COX-2 inhibitors dominate NSAID, since the only measurable difference between the 2 options is the risk of serious GI events.

We found that preferences for COX-2 inhibitors over NSAID are strongly influenced by the appeal of zero risk. Few patients surveyed in this study, when asked to be responsible for the full cost of medications, prefer COX-2 inhibitors over NSAID for a 50% risk reduction in serious GI adverse events, unless risk is eliminated. Older adults' willingness to pay for COX-2 inhibitors may reflect a misperception of the risk of toxicity associated with these medications.

REFERENCES

1. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. JAMA 2000;284:1247-55.
2. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-8.
3. Fraenkel L, Bogardus S, Concato J, Felson D. Unwillingness of rheumatoid arthritis patients to accept the risk of adverse effects. Rheumatology 2002;41:253-61.
4. Pullar T, Wright V, Feely M. What do patients and rheumatologists regard as an 'acceptable' risk in the treatment of rheumatic disease? Br J Rheumatol 1990;29:215-8.
5. O'Brien BJ, Elswood J, Calin A. Willingness to accept risk in the treatment of rheumatic disease. J Epidemiol Comm Health 1990;44:249-52.
6. Ho M, Lavery B, Pullar T. The risk of treatment: a study of rheumatoid arthritis patients' attitudes. Br J Rheumatol 1998;37:459-60.
7. Plous S. The psychology of judgement and decision making. New York: McGraw-Hill Inc.; 1993.
8. Tversky A, Kahneman D. The framing of decisions and the psychology of choice. Science 1981;211:453-8.
9. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
10. Wittink DR, Bergenstuen T. Forecasting with conjoint analysis. In: Armstrong JS, editor. Principles of forecasting: a handbook for researchers and practitioners. Norwell, MA: Kluwer Academic Publishers; 2001.
11. Wittink DR, Bergenstuen T. Forecasting with conjoint analysis. In: Armstrong JS, editor. Principles of forecasting: a handbook for researchers and practitioners. Norwell, MA: Kluwer Academic Publishers; 2001.
12. Johnson RM. Adaptive conjoint analysis. In: Proceedings, Sawtooth Software Conference on Perceptual Mapping, Conjoint Analysis, and Computer Interviewing. Ketchum, ID: Sawtooth, Software; 1987:253-65.
13. Cannon GW, Caldwell JR, Holt P, et al. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. Arthritis Rheum 2000;43:978-87.
14. Rothman AJ, Kiviniemi MT. Treating people with information: an analysis and review of approaches to communicating health risk information. Monogr Natl Cancer Inst 1999;25:44-51.
15. Mazur DJ, Hickam DH. Patients' interpretations of probability terms. J Gen Intern Med 1991;6:237-40.
16. Laudan L. The book of risks. New York: John Wiley & Sons, Inc.; 1994.
17. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929-33.
18. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241-9.
19. Singh G, Ramey DR, Triadafilopoulos G, Brown BW, Balise RR. GI SCORE: a simple self-assessment instrument to quantify the risk of serious NSAID-related GI complications in RA and OA [abstract]. Arthritis Rheum 1998;41 Suppl:S75.
20. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with emphasis on trial methodology. Semin Arthritis Rheum 1997;26:755-70.
21. Fraenkel L, Bogardus ST, Wittink DR. Understanding patient preferences for the treatment of lupus nephritis using adaptive conjoint analysis. Med Care 2001;39:1203-16.
22. Loewenstein GF, Hsee CK, Weber EU, Welch N. Risk as feelings. Psychol Bull 2001;127:267-86.