

## Variations in surgical rates in Quebec: Does access to teaching hospitals make a difference?

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**Objective:** To document the geographic variations in the rates of 10 common surgical procedures in Quebec and to examine the relation between surgical rates and level of access to teaching hospitals.

**Design:** Population-based rates standardized for age and sex were calculated from 1985–88 data from MED-ECHO (the provincial hospital discharge database) for each of the 32 community health districts (*départements de santé communautaire* [DSCs]) in Quebec. Variation across DSCs was analysed with the use of the ratio of the highest to the lowest rate, the coefficient of variation and the systematic component of variation. On the basis of an urbanization index designed by Statistics Canada, DSCs were classified as having a low, medium, high or very high level of access to teaching hospitals.

**Patients:** All Quebec residents except those whose DSC of residence could not be traced (accounting for no more than 1.7% of patients for any study procedure) and aboriginal people from northern Quebec.

**Surgical procedures studied:** Appendectomy, cesarean section, cholecystectomy, coronary artery bypass grafting (CABG), hysterectomy, inguinal hernia repair, prostatectomy, tonsillectomy with or without adenoidectomy, total hip replacement and varicose vein stripping.

**Results:** There was considerable systematic variation in the surgical rates for all 10 procedures. Cesarean section, the rates of which varied the least, still exhibited almost a twofold variation between the highest and lowest rates. The rates of tonsillectomy varied the most, by a factor of more than five. With a few exceptions there was relatively little relation between the rates of the procedures within the DSCs. The rates of appendectomy, cholecystectomy, hysterectomy and tonsillectomy tended to be lower in the DSCs containing teaching hospitals, whereas the reverse was true for CABG. For the other procedures the relation between the rates and the level of access to teaching hospitals was nonsignificant.

**Conclusions:** The overall consistency of the observed variations with those of previous studies invites a closer look at the practice patterns and the scientific basis of the clinical decisions associated with procedures showing high variations in rates. The lack of a systematic relation between the surgical rates and the level of access to teaching hospitals challenges the belief that remote regions are underserved with respect to the procedures studied.

**Objectif:** Documenter les variations géographiques dans les taux de 10 interventions chirurgicales courantes au Québec et examiner la relation entre les taux de chirurgie et le degré d'accès aux hôpitaux universitaires.

**Conception :** À partir des données de 1985–1988 de MED-ECHO (le fichier provincial des hospitalisations), les taux standardisés pour l'âge et le sexe, basés sur la population,

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ont été calculés pour chacun des 32 territoires de départements de santé communautaire (DSCs) du Québec. Les variations entre les DSCs ont été analysées en utilisant le ratio du taux le plus élevé sur le taux le plus bas, le coefficient de variation et la composante systématique de variation. À partir d'un indice d'urbanisation conçu par Statistique Canada, les DSCs ont été classés selon leur degré d'accès aux hôpitaux universitaires (faible, moyen, fort ou très fort).

**Patients :** Tous les résidents québécois, à l'exclusion de ceux dont le DSC de résidence était inconnu (pas plus de 1,7 % pour chaque opération) et des autochtones du nord du Québec.

**Interventions chirurgicales étudiées :** Appendicectomie, césarienne, cholécystectomie, pontage coronarien, hystérectomie, cure de l'hernie inguinale, prostatectomie, amygdalectomie avec ou sans adénoïdectomie, remplacement total de la hanche et ligature de veines variqueuses.

**Résultats :** On a trouvé des variations considérables et systématiques pour les 10 opérations. La césarienne, l'opération dont les taux variaient le moins, variait quand même par un facteur de près de deux entre le taux le plus fort et le taux le plus faible, alors que les taux d'amygdalectomie variaient le plus, soit par un facteur de plus de cinq. À quelques exceptions près, il y a relativement peu de relation entre les taux d'opérations à l'intérieur des DSCs. Les taux d'appendicectomie, de cholécystectomie, d'hystérectomie et d'amygdalectomie tendaient à être plus faibles dans les DSCs comprenant des hôpitaux universitaires, alors que l'inverse était vrai pour le pontage coronarien. Pour les autres opérations, il n'y avait pas de relation significative entre les taux et le degré d'accès aux hôpitaux universitaires.

**Conclusions :** La cohérence générale des variations documentées avec celles observées lors d'études antérieures invite à un examen plus approfondi des profils de pratique liés aux opérations à forte variation et de la base scientifique des décisions cliniques associées à ces variations. L'absence de relation systématique entre les taux de chirurgie et le degré d'accès aux hôpitaux universitaires remet en question la croyance qui veut que les régions éloignées sont mal desservies en ce qui concerne les opérations étudiées.

Over the past 25 years several studies have documented large and significant variations in population-based surgical rates among countries<sup>1-6</sup> as well as provinces, states, regions, counties, cities and hospital market areas.<sup>7-14</sup> Such findings have raised much concern about the possibility that people living in high-rate areas may be "overserved" (and hence unduly exposed to postoperative complications) and that those living in low-rate areas may not receive sufficient care.<sup>15</sup> Another concern has been that variations represent misallocation of resources in an era of cost containment.

Most studies of variations in surgical rates have been conducted in the United States and Europe. Some investigators have compared surgical rates across Canadian provinces;<sup>3,11,16</sup> others have focused on variations among areas within a few provinces.<sup>10,17-20</sup> No published study has looked at variations in Quebec.

Some important methodologic limitations can be found in a number of variation studies. First, rates for only 1 year have often been used, which entails the possibility that observed variations would not reflect a general trend. Second, studies that are not based on the whole population (e.g., Medicare and Medicaid patients in the United States) may be subject to serious bias. Third, procedures that are suitable for day surgery (e.g., hernia repair) — and their number is increasing — are under-

represented in studies based only on inpatient care.

Although the relation between surgical rates and several potential explanatory factors has been examined, the link between rates and access to teaching hospitals has rarely been studied. Thus, it is unclear whether better access to ultraspecialized care and proximity to scientific medical leaders and the most advanced knowledge make a difference in the use of surgery in a region. Moreover, in studies that examined access to teaching hospitals geographic units (e.g., counties) were merely divided into areas that contained a medical school and those that did not.<sup>10,20</sup> Such a simple classification may mask important differences between areas without a medical school. For example, remote areas and those adjacent to teaching areas must have quite different access to ultraspecialized care.

This study had two objectives. The first objective was to document the geographic variations in the rates of 10 common surgical procedures in Quebec while avoiding the methodologic limitations already outlined. The second objective was to examine the relation between surgical rates and access to teaching hospitals with the use of a four-level index of access.

## Methods

For planning purposes Quebec is divided into

32 community health districts (*départements de santé communautaire* [DSCs]). The population of each DSC was obtained from the 1986 Canadian census.<sup>21</sup> The population of the DSCs ranges from 45 000 to 415 000. The surgical rates were analysed on the basis of DSC of patient residence.

Data about operations and patients came from MED-ECHO, a universal hospital discharge database administered by the Quebec Department of Health and Social Services. This database contains all hospital discharge abstracts, including those for day surgery, for all short-stay hospitals in the province. Hospitals are required by law to provide these data. Many reliability checks are done by MED-ECHO staff, and corrections are made regularly to ensure correspondence between hospital records and the central database.<sup>22</sup> Confidentiality of patient information is guaranteed by the Quebec Department of Health and Social Services; no name or street address is included in the database available to researchers.

The surgical procedures examined were appendectomy, cesarean section, cholecystectomy, coronary artery bypass grafting (CABG), hysterectomy, inguinal hernia repair, prostatectomy, tonsillectomy with or without adenoidectomy, total hip replacement and varicose vein stripping (the specific procedure codes are available from the author upon request). These procedures were chosen for several reasons: most are frequently performed; they draw large resources; they represent a variety of patients (i.e., children, adult men and women, and elderly people); and they have been studied elsewhere, so that comparisons are possible.

For the 10 procedures all operations performed between Apr. 1, 1985, and Mar. 31, 1988, in patients of all age groups were available for study. Operations

performed in aboriginal people from northern Quebec and non-Quebec residents were excluded. Patients whose DSC of residence could not be traced were also excluded (accounting for no more than 1.7% of patients for any study procedure). For CABG and hip replacement one DSC, located on the border of Quebec and Ontario, had to be excluded because a large proportion of its patients are treated in Ontario and complete data for them were not available. Apart from these cases, a negligible proportion of patients (1% to 3%) undergo the study procedures outside Quebec. After exclusions, the number of cases over the 3 years ranged from 4377 for hip replacement to 54 328 for hysterectomy (Table 1).

### Analyses

For each study procedure except cesarean section surgical rates were calculated with the use of the DSC population (women only for hysterectomy and men only for prostatectomy) as the denominator and the number of operations performed in DSC residents as the numerator. For cesarean section the denominator was the total number of deliveries in the study period, as registered in the MED-ECHO database. Numbers of operations performed during the 3-year period were combined and the annual average was calculated to provide more stable rates. The rates were adjusted for age and sex with the indirect standardization method and the Quebec population as the reference population; for cesarean section crude rates were used.

The size of the geographic variations was estimated with the use of the ratio of the highest rate to the lowest rate, the coefficient of variation (standard deviation divided by the mean) and the systematic

Table 1: Variation in rates of surgical procedures among community health districts (*départements de santé communautaire* [DSCs]) in Quebec, 1985-88\*

Procedure	Annual average no. of operations	Provincial rate	Highest DSC rate	Lowest DSC rate	Ratio of highest to lowest rate	Coefficient of variation, %	Systematic component of variation, X 1000
Cesarean section	15 492	19.2	22.6	13.3	1.7	11	11
Cholecystectomy	16 819	257	383	167	2.3	16	22
Total hip replacement	1 459	24	35	14	2.5	21	23
Coronary artery bypass grafting (CABG)	3 229	50	67	22	3.0	18	29
Inguinal hernia repair	13 482	206	261	129	2.0	18	34
Hysterectomy	18 109	544	838	335	2.5	20	39
Appendectomy	8 735	134	261	96	2.7	25	43
Prostatectomy	8 687	271	356	158	2.3	23	54
Varicose vein stripping	4 019	62	84	32	2.6	24	60
Tonsillectomy (with or without adenoidectomy)	12 807	196	348	67	5.2	33	123

\*The rates are standardized for age per 100 000 women for hysterectomy, standardized for age per 100 000 men for prostatectomy, and standardized for age and sex per 100 000 population for the other procedures except cesarean section, for which the rates are per 100 deliveries.

component of variation (SCV), which is the estimate of the total variance minus the random component.<sup>4</sup> Although there is debate among methodologists as to the appropriate measures of variation and their properties (e.g., whether they are sensitive to the underlying rate and the area population size),<sup>9,23,24</sup> the three indicators used in this study are those most often employed in studies assessing geographic variations in use of health care services. Details about the characteristics of these measures are available elsewhere.<sup>3,4,9,23,24</sup>

An index of access to teaching hospitals was adapted from a classification used by Statistics Canada to rate the degree of urbanization of a region.<sup>25,26</sup> The initial six categories (1 rural, 2 semiurban, 3 nonuniversity fringe, 4 nonuniversity core, 5 university fringe and 6 university core) were reduced to four by combining categories 1 and 2 and categories 3 and 4. With this index DSCs were grouped into four categories: low level of access to teaching hospitals (remote and mainly rural DSCs), medium level of access (DSCs in intermediate regions), high level of access (suburban DSCs adjacent to DSCs containing teaching hospitals) and very high level of access (DSCs containing teaching hospitals).

The relation between surgical rates and access to teaching hospitals was examined by means of Somers' D correlation coefficient (asymmetric, with rates as the dependent variable). This coefficient is more appropriate and more conservative than the Pearson coefficient when one of the variables is ordinal (the level of access to teaching hospitals) and one variable is considered the dependent variable (the surgical rates).<sup>27</sup>

All analyses were done with SPSS software.<sup>28</sup>

## Results

Table 1 summarizes the variations among the 32 DSCs in the rates of the 10 surgical procedures studied. The procedures are ranked in ascending order of variation according to the SCV score.

Considerable variation was found in the surgical rates among the DSCs for all the procedures. However, the extent of variation differed greatly from one procedure to another. Cesarean section, the rates of which varied the least, still exhibited almost a twofold variation between the highest rate (22.6%) and the lowest rate (13.3%). The rates of tonsillectomy varied the most, by a factor of more than five. For the other procedures the ratio of the highest to the lowest rate ranged from 2.0 to 3.0. The statistical significance of the differences in rates across the DSCs was examined with the use of  $\chi^2$  tests ( $df = kDSCs - 1$ ). The test was significant ( $p < 0.01$ ) for all procedures (data not shown). However, since the whole population of patients rather than a sample was used, rates can be taken as population parameters, and the  $\chi^2$  test is less relevant.

Despite its wide use in previous studies and its intuitive meaning, the ratio of the highest to the lowest rate is generally considered statistically unstable and unreliable. Thus, the more appropriate coefficient of variation and SCV were also presented. Both measures, but especially the SCV, confirmed that for some procedures the rates varied much more than for others.

There was relatively little relation between the surgical rates within the DSCs. Only 13 of the 45 Pearson correlation coefficients were significant (Table 2). Eight coefficients were low, ranging from 0.31

Table 2: Pearson correlation between the surgical rates

Procedure	Procedure; coefficient								
	Cesarean section	Cholecystectomy	Total hip replacement	CABG	Inguinal hernia repair	Hysterectomy	Appendectomy	Prostatectomy	Varicose vein stripping
Cholecystectomy	0.07								
Total hip replacement	0.01	-0.05							
CABG	-0.26	-0.10	0.26						
Inguinal hernia repair	0.31*	-0.34*	-0.25	0.07					
Hysterectomy	0.18	0.60†	-0.07	-0.40*	-0.22				
Appendectomy	-0.12	0.53†	0.50†	0.03	-0.28	0.49†			
Prostatectomy	0.10	-0.21	-0.21	0.09	0.32*	-0.14	-0.34*		
Varicose vein stripping	-0.01	0.12	-0.22	-0.07	0.39*	0.10	0.08	0.29	
Tonsillectomy (with or without adenoidectomy)	0.19	0.28	-0.17	-0.47†	0.08	0.37*	0.13	-0.34*	0.03

\* $p < 0.05$ .  
† $p < 0.01$ .

to 0.40, and the others did not exceed 0.60. This means that, in general, the DSCs did not have consistently high or low rates across the procedures.

The relation between the level of access to teaching hospitals and the surgical rates varied considerably across the procedures (Table 3). For five procedures (cesarean section, total hip replacement, inguinal hernia repair, prostatectomy and varicose vein stripping) the correlations were practically null or nonsignificant. For appendectomy, cholecystectomy, hysterectomy and tonsillectomy the rates tended to be significantly higher in the DSCs with a lower level of access to teaching hospitals (i.e., in remote or intermediate regions). The only procedure for which there was a significant, although low, positive correlation between the rate and the level of access to teaching hospitals was CABG.

Beyond the simple presence or absence of significant correlations between the rates and the level of access to teaching hospitals, there were wide variations in the surgical rates within each of the four categories of DSCs (see the standard deviations in Table 3). But in general, except for cesarean section, this "within-group" variation tended to be lower in the DSCs with medical schools (very high access level) than in those with a low or medium level of access to university-affiliated hospitals. One DSC containing a medical school had an unusually low cesarean section rate; when this DSC was excluded, this observation about within-group variation was also true for cesarean section.

## Discussion

Although the variations in the surgical rates among the 32 DSCs for all 10 study procedures were large, previous studies have shown even greater variations.<sup>4,10,14</sup> These dissimilar results may reflect true differences in health care organization and financing; however, disparities in methods may account for part of the observed differences.

Unlike this study, in which 3 years of data were combined, other studies have given rates calculated on the basis of data for only 1 year.<sup>10,11,20</sup> Other investigators have used smaller geographic units than the Quebec DSCs.<sup>13,14</sup> Both methods are likely to produce less stable rates and larger variations than the ones found in this study.

Despite the greater between-area variation in this study, the ranking of variations is similar to that in other studies. For example, among the surgical procedures most frequently studied, rates of cholecystectomy and inguinal hernia repair usually have been shown to vary little across areas, whereas rates of hysterectomy and prostatectomy vary more, and tonsillectomy is among the most variable of procedures.<sup>4,9,14,29,30</sup> Rates of varicose vein stripping and cesarean section have been less often examined, but the findings from this study are in line with those of a few other studies showing that rates of the former procedure vary considerably,<sup>11,13</sup> whereas rates of the latter exhibit relatively low variation.<sup>31,32</sup> Although rates of total hip replacement have also rarely been

Table 3: Relation between the surgical rates and the level of access to teaching hospitals

Procedure	Somers' D correlation coefficient†	Level of access; mean rate (and standard deviation)*			
		Low (n = 6)	Medium (n = 11)	High (n = 6)	Very high (n = 9)
Cesarean section	-0.05	104 (11)	99 (11)	100 (9)	99 (14)
Cholecystectomy	-0.54§	119 (19)	104 (10)	101 (10)	91 (13)
Total hip replacement‡	0.02	108 (24)	98 (27)	110 (11)	101 (22)
CABG‡	0.30¶	96 (9)	99 (23)	110 (18)	108 (13)
Inguinal hernia repair	0.25	81 (16)	106 (12)	96 (22)	104 (15)
Hysterectomy	-0.64§	124 (23)	112 (15)	94 (8)	88 (14)
Appendectomy	-0.53§	122 (24)	107 (32)	100 (21)	85 (8)
Prostatectomy	0.19	93 (19)	100 (24)	98 (25)	103 (19)
Varicose vein stripping	0.01	87 (21)	109 (22)	105 (31)	92 (18)
Tonsillectomy (with or without adenoidectomy)	-0.37§	115 (51)	112 (37)	85 (8)	94 (21)

\*Rates are adjusted for age and sex (except for cesarean section) and expressed in ratio to the provincial rate X 100. The mean is weighted to account for the unequal population size of the DSCs.

†Asymmetric, with access as the independent variable and rate as the dependent variable.

‡For these procedures the DSC on the border of Quebec and Ontario (with a high level of access) was excluded because a large proportion of its patients are treated in Ontario.

§ $p < 0.01$ .

¶ $p < 0.05$ .

examined, at least one other study has documented moderately low variation for this procedure,<sup>7</sup> close to what was found here.

For appendectomy and CABG the results from this study differ somewhat from those in the literature. Whereas several investigators found that rates of appendectomy varied little,<sup>4,7,9,10,29,33</sup> only one study<sup>8</sup> showed the relatively high geographic variation for this procedure that was observed in Quebec. Variations in the rates of use of CABG are generally smaller in Quebec than elsewhere,<sup>7,32</sup> with one exception.<sup>34</sup>

To my knowledge this is the first study to examine the relation between surgical rates and level of access to teaching hospital care with a four-level index of access. The use of such an index instead of the simpler teaching/nonteaching dichotomy brings out more clearly the relation between rates and level of access. It also helps uncover important nuances: the three subgroups of "nonteaching" DSCs did not all have higher or lower mean rates than the DSCs containing a medical school. Indeed, for five of the procedures studied, the mean rate for DSCs containing a medical school fell between the highest and the lowest mean rates for the three subgroups of nonteaching DSCs (Table 3).

No consistent relation between the rates and the level of access to teaching hospitals was found. However, four of the five significant correlations were negative, which indicates that the rates were lower in the areas with greater access to teaching hospitals. These results, which are consistent with those of other studies,<sup>10,20</sup> challenge the belief that remote or rural regions, which have lower access to teaching hospital care, are underserved compared with areas containing medical schools, because they have fewer surgeons and specialists per capita.<sup>35</sup> Only in the case of CABG, which is a highly complex procedure carried out almost exclusively in urban tertiary care teaching hospitals, was there a significant positive, although low, correlation between the surgical rate and the level of access.

Several factors may be associated with the lower rates observed in the DSCs containing teaching hospitals. First, it has been suggested that since university-affiliated hospitals are referral centres for the DSCs without teaching hospitals, they may have fewer resources to devote to the patients of their own area.<sup>10</sup> Second, surgeons in the DSCs with teaching hospitals may make less use of "conventional" surgery because they have access to alternative treatment strategies, including high technology. Third, as their level of specialization increases, physicians may use more diagnostic tests, thus avoiding surgery in less obvious cases.<sup>8</sup> Fourth, since teaching hospitals have access to the most up-to-date scientific knowledge, they may use surgery for differ-

ent and perhaps more restrictive indications than nonteaching hospitals. Although there is no hard evidence to support this hypothesis, it would be consistent with the findings of Roos, Roos and Henteleff<sup>9</sup> indicating that higher tonsillectomy rates are associated with the use of less stringent indications. Fifth, in remote regions where mainly "visiting" specialists perform some types of surgery, there may be a propensity to intervene earlier, "when the specialist is around," rather than wait and face possible problems when the specialist is not there.

Although the purpose of this study was not to examine in detail the determinants of the variations in surgical rates, some inferences may be made about the reasons for the variations observed. The study was conceived to minimize variation due to error and small samples. The SCV score, in particular, which is designed to remove the random component of variance,<sup>4</sup> helps reveal the existence of systematic variations in surgical rates among DSCs. Adjusting the surgical rates for age and sex limits the possibility that variations among DSCs could be due to regional differences in the rates of corresponding diseases. Differential morbidity not captured by this standardization process is unlikely to account for the large variations in rates observed here. Besides, some studies have shown that a small-area surgical rate is not correlated with the health status of the resident population.<sup>36,37</sup>

Other population characteristics, such as socioeconomic status, could explain some of the variation. However, the lack of correlation between the rates of the various procedures within the DSCs makes it unlikely that a socioeconomic bias existed for all study procedures. Patient preferences are another possibility, but they are difficult to measure, and to my knowledge no study has tested their relation with surgical rates.

A larger supply of health care resources within a DSC may be associated with higher surgical rates, although the results in this study and in others<sup>20</sup> tend to show that this does not hold true for areas with teaching hospitals. Although several investigators have reported positive correlations between surgical rates and resources, such as the number of physicians or surgeons,<sup>13,14,38,39</sup> others have found negative correlations.<sup>16,40</sup> However, the inconsistencies of these results and a closer look at the literature suggest that the resources-rates relation is specific to individual surgical procedures.<sup>8</sup> The lack of correlation between the rates of the various procedures studied here supports this idea that each type of surgery has its own dynamics of use.

This line of thought implies that a relevant analysis of the relation between rates and resources should be based on indicators specific to each type of procedure (e.g., the number of otolaryngologists for



tonsillectomy) rather than on global measures (e.g., the total number of physicians or specialists). It has been shown that the number of physicians who actually perform a given procedure in an area is a more sensitive indicator of surgical resources than more general and commonly used measures.<sup>19</sup> Such information should be taken into consideration in future analyses of the determinants of the variations in surgical rates.

The overall consistency between the rankings of the variations in rates of surgical procedures in this study and those of earlier studies supports the idea that when similarity in the level of variation of one surgical procedure is observed across countries or states, such variations cannot be due simply to differences in the characteristics of the populations or the health care systems. Instead, these variations would be typical of each procedure and would be related to the amount (or lack) of scientific knowledge about appropriate indications and efficacy.<sup>4</sup> Thus, it has been proposed that variations in the use of medical and surgical interventions would be explained, in several instances, by differences in what authors have called "medical opinions," "practice style" or "approaches to treatment."<sup>10,41-43</sup>

Although further analysis of the factors associated with the variations observed in Quebec would be warranted, the general consistency of the findings in this study with those of studies conducted in other jurisdictions with different methods makes lack of medical consensus the most plausible explanation for the variations. The smaller variations observed within the subgroup of DSCs with teaching hospitals also tend to support this proposition: teaching hospitals all have access, at least in theory, to the most recent scientific knowledge, whereas this knowledge always takes longer to reach nonteaching hospitals, especially in remote regions. This leaves more room for differing medical opinions in the latter hospitals. Several strategies could be used to improve and disseminate the knowledge base of medical practice: outcome evaluation studies, consensus conferences, clinical guidelines development and continuing medical education.

Given that several medical specialties are represented by the procedures studied and that these procedures account for an important proportion of the workload within each specialty, the results support the idea that variation in the use of health care services is a widespread phenomenon and is not limited to a few procedures or a few practitioners located in particular areas. It was beyond the scope of this study to assess whether surgical intervention rates were too low in some areas or too high in others. However, the findings and their consistency with previous work warrant a closer look by the medical profession at the practice patterns related to

the high-variation procedures and at the scientific basis of the clinical decisions associated with these variations.

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**THERAPEUTIC CLASSIFICATION** Mucosal Protective Agent

**INDICATIONS** CYTOTEC (misoprostol) is indicated for the prevention of NSAID-induced gastric ulcers. Patients at high risk of developing NSAID-induced complications and who may require protection include: • Patients with a previous history of ulcer disease or a significant gastrointestinal event. • Patients over 60 years of age. • Patients judged to be at risk because of general poor health, severe concomitant medical disease, or patients who are poor surgical risks. • Patients disabled by joint symptoms (e.g., HAQ Disability Index Score >1.5) or those with severe systemic manifestations of arthritis. • Patients taking other drugs known to damage or exacerbate damage to the gastrointestinal tract such as corticosteroids or anticoagulants. • Patients taking a high dosage or multiple NSAIDs, including those available Over-The-Counter. The risk of NSAID-induced complications may be highest in the first three months of NSAID therapy. CYTOTEC is also indicated for the treatment of NSAID-induced gastric ulcers (defined as  $\geq 0.3$  cm in diameter) and for the treatment of duodenal ulcers.

**CONTRAINDICATIONS** Known sensitivity to prostaglandins, prostaglandin analogues, or excipients (microcrystalline and hydroxypropyl methylcellulose, sodium starch glycolate and hydrogenated castor oil). Contraindicated in pregnancy. (See CLINICAL PHARMACOLOGY.) Women should be advised not to become pregnant while taking CYTOTEC (misoprostol). If pregnancy is suspected, use of the product should be discontinued.

**WARNINGS** Women of childbearing potential should employ adequate contraception (i.e., oral contraceptives or intrauterine devices) while receiving CYTOTEC (misoprostol). (See CONTRAINDICATIONS.) **Nursing Mothers:** It is unlikely that CYTOTEC is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, CYTOTEC should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants. **Pediatric Use:** Safety and effectiveness in patients below the age of 18 have not been established.

**PRECAUTIONS** **Selection of Patients:** Caution should be used when using symptomatology as the sole diagnostic and follow-up procedure, since CYTOTEC (misoprostol) has not been shown to have an effect on gastrointestinal pain or discomfort. Before treatment is undertaken, a positive diagnosis of duodenal ulcer or NSAID-induced gastric ulcer should be made. The general health of the patient should be considered. Misoprostol is rapidly metabolized by most body tissues to inactive metabolites. Nevertheless, caution should be exercised when patients have impairment of renal or hepatic function. (See CLINICAL PHARMACOLOGY.) **Pharmacokinetics:** Diarrhea: Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as irritable bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if CYTOTEC is prescribed. **Use in Elderly and Renally Impaired:** Considerations for Dosage Adjustment: In subjects over 64 years of age or those who are renally impaired the pharmacokinetics may be affected, but not to a clinically significant degree. (See DOSAGE AND ADMINISTRATION.) No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 mcg QID) is recommended. **Drug Interactions:** The serum protein binding of misoprostol acid (the active metabolite of misoprostol) was not affected by: indomethacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, acetaminophen, ibuprofen, chlorpromazine, and hydrochlorothiazide. Salicylic acid (300 mcg/ml) lowered the protein binding of misoprostol from 84% to 52%; this is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short. In laboratory studies, misoprostol has shown no significant effect on the cytochrome P450 - linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolized by this system. No drug interactions attributable to misoprostol have been observed to date. (See CLINICAL PHARMACOLOGY.) Some prostaglandins and prostaglandin analogues have the capacity to produce hypotension through peripheral vasodilation. The results of clinical trials to date indicate that CYTOTEC has not produced hypotension at dosages effective in promoting the healing of ulcers. Nevertheless, CYTOTEC should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g., cerebral vascular disease or coronary artery disease. Epileptic seizures have been reported with prostaglandins and prostaglandin analogues administered by routes other than oral. Therefore, misoprostol tablets should be used in known epileptics only when their epilepsy is adequately controlled and then only when expected benefits outweigh potential risks. Symptomatic responses to CYTOTEC do not preclude the presence of gastric malignancy.

**ADVERSE REACTIONS** **Gastrointestinal:** In subjects receiving CYTOTEC (misoprostol) 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea, abdominal pain and flatulence. The average incidences of these events were 11.4%, 6.8% and 2.9%, respectively. In clinical trials using a dosage regimen of 400 mcg bid, the incidence of diarrhea was 12.6%. The events were usually transient and mild to moderate in severity. Diarrhea, when it occurred, usually developed early in the course of therapy, was self limiting and required discontinuation of CYTOTEC in less than 2% of the patients. The incidence of diarrhea can be minimized by adjusting the dose of CYTOTEC, by administering after food, and by avoiding co-administration of CYTOTEC with magnesium-containing antacids. **Gynecological:** Women who received CYTOTEC during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). **Elderly:** There were no significant differences in the safety profile of CYTOTEC in approximately 500 ulcer patients who were 65 years of age or older, compared with younger patients. Confusion has been reported in a small number of patients in our post marketing surveillance of CYTOTEC. **Incidence greater than 1%:** In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving CYTOTEC and may be causally related to the drug: nausea (3.2%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%) and constipation (1.1%). However, there were no clinically significant differences between the incidences of these events for CYTOTEC and placebo.

**DOSAGE AND ADMINISTRATION** **Treatment and Prevention of NSAID-Induced Gastric Ulcers:** The recommended adult oral dosage of CYTOTEC (misoprostol) for the prevention and treatment of NSAID-induced gastric ulcer is 400 to 800 mcg a day in divided doses. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate, CYTOTEC and NSAIDs are to be taken simultaneously. CYTOTEC should be taken after food. **Duodenal Ulcer:** The recommended adult oral dosage of CYTOTEC (misoprostol) for duodenal ulcer is 800 mcg per day for 4 weeks in two or four equally divided doses (i.e., 200 mcg tid or 400 mcg bid). The last dose should be taken at bedtime with food. Antacids (alkalinity based) may be used as needed for relief of pain. Treatment should be continued for a total of 4 weeks unless healing in less time has been documented by endoscopic examination. In the small number of patients who may not have fully healed after 4 weeks, therapy with CYTOTEC may be continued for a further 4 weeks. **Use in Elderly and Renally Impaired:** Consideration for Dosage Adjustment: Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of  $t_{1/2}$ ,  $C_{max}$  and AUC compared to normals. There was no clear correlation between degree of impairment and AUC. In subjects over 64 years of age the pharmacokinetics may be affected. In both patient groups the pharmacokinetic changes are not clinically significant. No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 mcg QID) is recommended.

**AVAILABILITY** CYTOTEC (misoprostol) 200 mcg tablets are white to off-white, scored, hexagonal with SEARLE 1461 engraved on one side available in bottles of 120 and 500 tablets. CYTOTEC 100 mcg tablets are white to off-white, round tablets with SEARLE engraved on one side and CYTOTEC on the other available in bottles of 100 tablets.

Store below 30°C (86°F)

Pharmacist: Dispense with Patient Insert.

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