Safety of Capsaicin Cough Challenge Testing*

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Background: Capsaicin, the pungent extract of red peppers, has achieved widespread use in clinical research because it induces cough in a dose-dependent and reproducible manner. Although > 2 decades of experience has led investigators to consider capsaicin cough challenge testing a safe diagnostic modality, this issue has not been specifically addressed in the literature. Study objectives: To review the published experience with capsaicin inhalation challenge testing in terms of safety.

Design: Literature review and personal communication with study authors.

Setting: Academic medical center.

Results: One hundred twenty-two published studies since 1984 described 4,833 subjects (4,374 adults, 459 children) undergoing capsaicin cough challenge, with no serious adverse events reported. Subjects included healthy volunteers as well as patients with asthma, COPD, pathologic cough, and other respiratory conditions. Minor complaints described in a small fraction of studies consisted mainly of transient throat irritation. Personal communication with the authors of > 90% of the studies confirmed an absence of any serious adverse events. Furthermore, these investigators have performed thousands of additional capsaicin challenge studies not reported in the literature, also without any associated serious adverse events.

Conclusions: A review of the 20-year clinical experience has failed to uncover a single serious adverse event associated with capsaicin cough challenge testing in humans. Given the need for better antitussive therapies, capsaicin represents a vital component of future scientific inquiry in the field of cough. (CHEST 2005; 128:196–202)

Key words: adverse effects; capsaicin; capsicum; cough; cough challenge studies; safety; side effects

Abbreviation: sGaw = specific airways conductance

Capsaicin, the pungent extract of red peppers (Capsicum fruit), has achieved widespread use in clinical research because it induces cough, in humans, in a dose-dependent and reproducible fashion. In > 2 decades of clinical experience, capsaicin has arguably become the preferred agent for measurement of cough reflex sensitivity because of its favorable side effect profile, minimal if any tachyphylaxis, and the correlation of capsaicin sensitivity to the presence of pathologic cough. Although the vast clinical experience with this agent has led investigators to consider capsaicin cough challenge testing a safe diagnostic modality, this issue has not been specifically addressed in the literature. The purpose of the present study, therefore, was to review the published experience with capsaicin cough challenge testing in terms of safety.

Materials and Methods

In September 2003, we performed a National Library of Medicine (PubMed) search of the English-language literature, limited to human studies, using the search terms “cough” and “capsaicin.” The search yielded a total of 163 publications, the abstracts of which were evaluated to exclude review articles, editorials, and other works that did not report original data. After this editing process, 122 studies remained that reported original data employing capsaicin cough challenge testing. The full articles of these studies were reviewed to determine the number of subjects evaluated, and whether any adverse events associated with the use of inhaled capsaicin were reported. Because the lack of reported adverse events in an article does not necessarily imply their absence, we personally contacted the authors of all studies to absolutely confirm that no serious side effects of capsaicin cough challenge testing had occurred. This information was obtained either through verbal or electronic communication.
RESULTS

The 122 published studies that we evaluated described a total of 4,833 subjects (4,374 adults and 459 children) undergoing capsaicin cough challenge testing.1–122 Study subjects included healthy volunteers as well as patients with asthma, COPD, and other diagnoses (Table 1).

No serious adverse reactions to capsaicin inhalation challenge were reported. In the small fraction of studies that mentioned any adverse reactions to capsaicin inhalation, these were limited to minor complaints, most commonly transient throat irritation. In addition, three studies described nine subjects, seven of whom were asthmatic, with transient asymptomatic bronchoconstriction after capsaicin inhalation, as measured by spirometry85,110 and specific airways conductance (sGaw).2 One study122 specifically evaluating bronchoconstriction after capsaicin inhalation demonstrated a dose-dependent fall in sGaw that lasted < 60 s, and was similar in asthmatics and healthy volunteers. Subjects were described as reporting some degree of retrosternal discomfort accompanying cough at higher concentrations of inhaled capsaicin, the severity of which was not related to the magnitude of the fall in sGaw. Other studies3,14,47,59,63,86,97 performed in asthmatics and healthy volunteers were unable to demonstrate a significant effect of inhaled capsaicin on FEV1.

The only studies12,22,34 reporting that capsaicin induced symptoms other than cough and transient throat irritation or retrosternal discomfort were limited to those of one investigator, who has identified a subgroup of predominantly nonasthmatic subjects with a sensitivity to strong scents, chemicals, and other environmental agents. This group has been termed as having sensory hyper-reactivity.12,22,34 When some of these subjects undergo capsaicin cough challenge testing, the same symptoms develop as happens from exposure to numerous environmental triggers, such as nasal and ocular irritation, rhinorrhea, hoarseness, phlegm production, and dyspnea. However, these symptoms are always transient, have always been experienced prior to initial capsaicin challenge, and are never more severe after capsaicin inhalation than when induced by environmental triggers.

In addition to reviewing the 122 articles for reports of adverse reactions associated with capsaicin challenge testing, we were able to personally contact the authors of 109 of the 122 studies (89%), all of whom confirmed that there in fact had been no serious adverse events associated with capsaicin inhalation. This personal verification accounts for 4,371 of the 4,833 published capsaicin cough challenge studies (90.4%). Furthermore, in our personal communications we learned that several thousand additional subjects have been tested, although not reported in published studies, without associated adverse effects. This additional number of subjects far outweighs the possible duplication of study subjects reported in the literature. In these additional thousands of unpublished challenge studies, all investigators confirmed the absence of any serious adverse events associated with capsaicin inhalation.

Table 1—Subjects in Published Studies Having Undergone Capsaicin Cough Challenge Testing

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td></td>
<td>2,671</td>
</tr>
<tr>
<td>Pathological cough</td>
<td></td>
<td>788</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td>538</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td>162</td>
</tr>
<tr>
<td>Hypertensives on angiotensin-converting enzyme inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td></td>
<td>94</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>Acute upper respiratory tract infection</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Cervical spinal cord injury</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Heart-lung transplant patients</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>4,374</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td></td>
<td>196</td>
</tr>
<tr>
<td>Pathologic cough</td>
<td></td>
<td>133</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>459</td>
</tr>
</tbody>
</table>

*Total exceeds sum of subgroups because of overlap between subgroups.

DISCUSSION

Our review has failed to uncover a single serious adverse event associated with the use of inhaled capsaicin in 4,833 subjects described in published studies over the past 2 decades. We were able to positively confirm the lack of adverse events through personal communication with investigators whose work accounted for > 90% of the subjects described in the literature. Furthermore, our interactions with study authors evinced the fact that several thousand additional subjects have been tested, although not reported in published studies, without associated adverse effects. This additional number of subjects far outweighs the possible duplication of study subjects reported in the published literature, of which we are unaware.

The robust record of safety of capsaicin cough challenge applies not only to healthy adults and children, but also to adult and pediatric patients with asthma, COPD, pathologic cough, and other condi-
tions. Although a few studies\(^2,85,110,122\) reported a handful of cases of asymptomatic bronchoconstriction when measured by FEV\(_1\) or sGaw, no known clinically significant occurrences of bronchospasm or exacerbations of asthma have been described in association with capsaicin challenge. In fact, asthmatics without cough do not differ from healthy volunteers in terms of cough reflex sensitivity to capsaicin, thus illustrating that cough and bronchial responsiveness are distinct phenomena mediated through distinct neural pathways.\(^21\)

Many of the studies cited in this review involved not one but multiple capsaicin inhalation challenges performed over a period of days to weeks. The lack of associated adverse effects supports the safety of capsaicin cough challenge with repeated testing over time. The authors have performed multiple placebo-controlled, crossover studies\(^21,25,41,65\) that entailed four cough challenges per subject. After several years of follow-up, to our knowledge, no adverse effects in any subject have become evident.

Two studies have specifically examined the long-term respiratory effects of occupational exposure to capsaicin. In one study,\(^110\) 22 hot (Capsicum) pepper workers in a spice manufacturing facility were compared to 19 unexposed workers. The two groups did not differ in terms of FEV\(_1\) and FVC. The Capsicum-exposed workers complained of cough more than control subjects, and had a higher cough threshold, ie, diminished sensitivity to capsaicin, compared to nonexposed workers. However, the higher cough threshold in the exposed workers was significantly related to male gender and cigarette smoking, both factors that have been shown to be associated with diminished cough reflex sensitivity to capsaicin,\(^5,52\)

Another study\(^123\) evaluated 25 male Sri Lankan chili grinders with an average duration of exposure of 6.6 years (range, 3 months to 20 years). Pulmonary function measurements were performed before and after a Monday work shift, and compared to a control group. There were no significant across-shift changes in pulmonary function indexes in the chili grinders compared to control subjects, nor were there any significant differences in preshift measurements between the two groups.

The literature also contains a few case reports of respiratory complications after exposure to commercially available pepper spray, a riot-control and self-defense agent containing oleoresin capsaicin. One report\(^124\) described the occurrence of reactive airways dysfunction syndrome in a previously healthy subject who had been exposed to a product containing 1% oleoresin capsaicin as well as 1% orthochlorobenzalmonitride in a solvent blend containing an ultraviolet dye. Orthochlorobenzalmonitride is a potent lacrimating agent and upper respiratory irritant. Another case report\(^125\) described an 11-year-old boy who acquired noncardiogenic pulmonary edema and severe croup after deliberate inhalation of a product containing 5% oleoresin capsaicin as well as the propellants isobutane/propane and two organic solvents: methyl-isobutylketone, which has been reported to cause upper respiratory tract irritation, and tetrachloroethylene, which may produce pulmonary edema. Given the documented safety of highly purified capsaicin inhalation cough challenge in medical research, it appears likely that these reported events reflect the toxicity of noncapsaicin components of the pepper spray mixtures.

One review of the experience with pepper spray by police forces subduing aggressive individuals concluded that the agent was a relatively safe weapon with small risk of causing acute physical harm.\(^126\) All but possibly one of the associated mortalities were deemed unrelated to the use of pepper spray. A study\(^127\) of 81 individuals presenting to an emergency department after oleoresin capsicum aerosol exposure found that none of the patients required hospitalization due to toxicity. More recently, a randomized, cross-over, controlled trial\(^128\) was performed to assess the effect of oleoresin capsicum pepper spray inhalation, alone or combined with restraint, on respiratory function. Pepper spray exposure did not result in abnormal spirometry findings, hypoxemia, or hypoventilation when compared with placebo.

Some previous animal and cell culture studies\(^129–131\) have suggested that capsaicin may be mutagenic and/or tumorigenic. However, subsequent studies\(^132–134\) have failed to demonstrate such capsaicin-induced effects, and have even demonstrated a chemoprotective effect of capsaicin against vinyl carbamate and N-nitrosodimethylamine-induced mutagenesis and tumorigenesis.\(^135\) The capsaicin tested in most previous studies was derived from pepper plant extracts, thus making it likely that varying degrees of purity and possibly diverse impurity profiles were examined.\(^136\) A more recent study\(^136\) evaluated the genotoxic potential of pure, synthetic transcapsaicin, the only naturally occurring geometric isomer of capsaicin, using four genotoxicity assays widely used to evaluate drug substances. The authors of that trial\(^136\) concluded that the genotoxic potential of pure transcapsaicin is very low.

More than 2 decades of clinical experience has demonstrated capsaicin inhalation challenge to be an extremely safe research tool. Given the enormous need for more effective antitussive therapies, capsaicin represents a vital component of future investigation in the field of cough.
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