Clinical Policy Bulletin: Carbogen Inhalation Therapy

Number: 0428

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers carbogen inhalation therapy for the treatment of the following indications experimental and investigational because the effectiveness of this treatment has not been established by the peer-reviewed medical literature (not an all-inclusive list).

- Bladder cancer
- Central retinal artery occlusion
- Cervical cancer
- Head and neck cancers (e.g., laryngeal, lip, mucosal melanoma, nasopharyngeal, oral cavity, paranasal sinuses, and salivary gland cancers)
- Optic nerve damage/degeneration
- Prostate cancer
- Retinal artery occlusion
- Seizures
- Stroke
- Sudden hearing loss.

Background

Sudden hearing loss (SHL) is defined as sensorineural hearing loss of 30 decibels or more in 3 contiguous frequencies that develops in less than 3 days. In most patients with SHL, hearing loss occurs within much less than 3 days. Although a number of disease processes can produce similar hearing loss, true SHL is idiopathic in nature. Males and females are evenly affected by SHL, and either ear is equally vulnerable. The hearing loss is unilateral in about 90 % of patients. In some patients, the profound loss in hearing may lessen, and in some cases, completely recover over a period of days or weeks. Currently, there is no definitive practice guideline for the treatment of SHL. Steroid therapy appears to be the only medical treatment proven to have a significant beneficial effect in selected patients with idiopathic SHL.

Various agents designed to enhance cochlear circulation and oxygenation has been advocated for the treatment of SHL. These include plasma expanders, anti-platelet agents, anti-coagulants, vasodilators, and carbogen gas (5 % carbon dioxide and 95 % oxygen). It has been suggested that carbogen inhalation therapy is effective in treating patients with high-frequency-sloping (from pure-tone audiogram) hearing impairment. However, clinical studies of carbogen inhalation therapy have demonstrated no improvement in rates of recovery from SHL than the rate of spontaneous recovery. A
systematic review of the evidence of the use of carbogen gas for treatment of sudden deafness (Hender et al, 2002) concluded that "it is reasonably safe to conclude that carbogen gas inhalation is no more effective than heparin or 'standard care' in patients with idiopathic sudden sensorineural hearing loss".

Ashkanian et al (2009) stated that hyperoxic therapy for cerebral ischemia reduces cerebral blood flow (CBF) principally from the vasoconstrictive effect of oxygen on cerebral arterioles. Based on a recent study in normal volunteers, these researchers claim that the vasodilatory effect of carbon dioxide predominates when 5 % CO(2) is added to inhaled oxygen (the mixture known as carbogen). These investigators measured CBF by positron emission tomography (PET) during inhalation of test gases (O(2), carbogen, and atmospheric air) in healthy volunteers (n = 10) and in patients with occlusive carotid artery disease (n = 6). Statistical comparisons by an additive ANOVA model showed that carbogen significantly increased CBF by 7.51 + or - 1.62 ml/100 g/min while oxygen tended to reduce it by -3.22 + or - 1.62 ml/100 g/min. A separate analysis of the hemisphere contralateral to the hypo-perfused hemisphere showed that carbogen significantly increased CBF by 8.90 + or - 2.81 ml/100 g/min whereas oxygen inhalation produced no reliable change in CBF (-1.15 + or - 2.81 ml/100 g/min). In both patients and controls, carbogen was as efficient as oxygen in increasing Sa(O2) or PaO(2) values. The findings of this study demonstrated that concomitant increases of CBF and Sa(O2) are readily obtained with carbogen, while oxygen increases only Sa(O2). Thus, carbogen improves oxygen transport to brain tissue more efficiently than oxygen alone. The authors concluded that further studies with more subjects are, however, needed to investigate the applicability of carbogen for long-term inhalation and to assess its therapeutic benefits in acute stroke patients.

Tolner et al (2011) examined if inhaling 5 % CO(2) can be used to suppress seizures in epilepsy patients. The effect of CO(2) on cortical epileptic activity accompanying behavioral seizures was studied in rats and non-human primates, and based on these data, preliminary tests were carried out in humans. In freely moving rats, cortical afterdischarges paralleled by myoclonic convulsions were evoked by sensorimotor cortex stimulation. Five percent CO(2) was applied for 5 mins, 3 mins before stimulation. In macaque monkeys, hypercarbia was induced by hypoventilation while seizure activity was electrically or chemically evoked in the sensorimotor cortex. A total of 7 patients with drug-resistant partial epilepsy were examined with video-electroencephalography and received 5 % CO(2) in medical carbogen shortly after electrographic seizure onset. In rats, 5 % CO(2) strongly suppressed cortical afterdischarges, by approximately 75 %, whereas responses to single-pulse stimulation were reduced by about 15 %. In macaques, increasing pCO(2) from 37 mm Hg to 44 - 45 mm Hg (corresponding to inhalation of 5 % CO(2) or less) suppressed stimulation-induced cortical afterdischarges by about 70 % and single, bicuculline-induced epileptiform spikes by approximately 25 %. In a pilot trial carried out in 7 patients, a rapid termination of electrographic seizures was observed despite the fact that the application of 5 % CO(2) was started after seizure generalization. The authors concluded that 5 % CO(2) has a fast and potent anti-convulsant action. The present data suggested that medical carbogen with 5 % CO(2) can be used for acute treatment to suppress seizures in epilepsy patients. The findings of this small, pilot study need to be validated by well-designed studies.

Cugati et al (2013) stated that central retinal artery occlusion (CRAO) is an ocular emergency and is the ocular analog of cerebral stroke. It results in profound, usually monocular vision loss, and is associated with significant functional morbidity. The risk factors for CRAO are the same atherosclerotic risk factors as for stroke and heart disease. As such, individuals with CRAO may be at risk of ischemic end organ damage such as a cerebral stroke. Therefore, the management of CRAO is not only to restore vision, but at the same time to manage risk factors that may lead to other vascular conditions. There are a number of therapies that has been used in the treatment of CRAO in the past. These include carbogen inhalation, acetazolamide infusion, ocular massage and paracentesis, as well as various vasodilators such as intravenous glyceryl trinitrate. None of these "standard agents" had been shown to alter the natural history of disease definitively. There has been recent interest shown in the use of thrombolytic therapy, delivered either intravenously or intra-arterially by direct catheterization of the ophthalmic artery. While a number of observational series have shown that the recovery of vision can be quite dramatic, 2 recent randomized controlled trials have not demonstrated efficacy. On
the contrary, intra-arterial delivery of thrombolytic may result in an increased risk of intra-cranial and systemic hemorrhage, while the intravenous use of tissue plasminogen activator was not shown to be effective within 24 hrs of symptom onset. Nevertheless, both of these studies have shown one thing in common, and that is for treatment to be effective in CRAO, it must be deployed within a short time window, probably within 6 hrs of symptom onset. Therefore, while CRAO is a disease that does not have a treatment, nevertheless it needs to follow the same principles of treatment as any other vascular end organ ischemic disease. That is, to attempt to re-perfuse ischemic tissue as quickly as possible and to institute secondary prevention early.

Furthermore, an UpToDate review on “Central and branch retinal artery occlusion” (Hedges, 2013) states that “A mixture of 95 percent oxygen and 5 percent carbon dioxide (Carbogen) can be provided in an attempt to induce vasodilation and improve oxygenation. However, this is difficult to obtain in most hospitals on an urgent basis, and published reports are not supportive of its efficacy”.

Ohlraun et al (2013) noted that 2 to 8 % of all children aged between 6 months and 5 years have febrile seizures. Often these seizures cease spontaneously, however depending on different national guidelines, 20 to 40 % of the patients would need therapeutic intervention. For seizures longer than 3 to 5 minutes application of rectal diazepam, buccal midazolam or sublingual lorazepam is recommended. Benzodiazepines may be ineffective in some patients or cause prolonged sedation and fatigue. Pre-clinical investigations in a rat model provided evidence that febrile seizures may be triggered by respiratory alkalosis, which was subsequently confirmed by a retrospective clinical observation. Further, individual therapeutic interventions showed that a pCO2-elevation via re-breathing or inhalation of 5 % CO2 instantly stopped the febrile seizures. These researchers presented the protocol for an interventional clinical trial to test the hypothesis that the application of 5 % CO2 is safe and effective to suppress febrile seizures in children. The CARDIF (CARbon DIoxide against Febrile seizures) trial is a mono-centric, prospective, double-blind, placebo-controlled, randomized study. A total of 288 patients with a life history of at least 1 febrile seizure will be randomized to receive either carbogen (5 % CO2 plus 95 % O2) or placebo (100 % O2). As recurrences of febrile seizures mainly occur at home, the study medication will be administered by the parents through a low-pressure can fitted with a respiratory mask. The primary outcome measure is the effectiveness of carbogen to interrupt febrile seizures. As secondary outcome parameters, these researchers assess safety, practicability to use the can, quality of life, contentedness, anxiousness and mobility of the parents. The authors stated that the CARDIF trial has the potential to develop a new therapy for the suppression of febrile seizures by redressing the normal physiological state. This would offer an alternative to the currently suggested treatment with benzodiazepines. This study is an example of academic translational research from the study of animal physiology to a new therapy.

Janssens et al (2012) reported the results from a randomized trial comparing accelerated radiotherapy (AR) with accelerated radiotherapy plus carbogen inhalation and nicotinamide (ARCON) in laryngeal cancer. Patients with cT2-4 squamous cell laryngeal cancer were randomly assigned to AR (68 Gy within 36 to 38 days) or ARCON. To limit the risk of laryngeal necrosis, ARCON patients received 64 Gy on the laryngeal cartilage. The primary end-point was local control. Secondary end-points were regional control, larynx preservation, toxicity, disease-free survival, and overall survival. In a translational side study, the hypoxia marker pimonidazole was used to assess the oxygenation status in tumor biopsies. From April 2001 to February 2008, a total of 345 patients were accrued. After a median follow-up of 44 months, local tumor control rate at 5 years was 78 % for AR versus 79 % for ARCON (p = 0.80), with larynx preservation rates of 84 % and 87 %, respectively (p = 0.48). The 5-year regional control was significantly better with ARCON (93 %) compared with AR (86 %, p = 0.04). The improvement in regional control was specifically observed in patients with hypoxic tumors and not in patients with well-oxygenated tumors (100 % versus 55 %, respectively; p = 0.01). Accelerated radiotherapy and ARCON produced equal levels of toxicity. The authors concluded that despite lack of benefit in local tumor control for advanced laryngeal cancers, a significant gain in regional control rate, with equal levels of toxicity, was observed in favor of ARCON. The poor regional control of patients with hypoxic tumors is specifically countered by ARCON treatment.
Eustace and colleagues (2013) examined if a 26-gene hypoxia signature predicted benefit from hypoxia-modifying treatment in both bladder and laryngeal cancers. Samples were available from 157 T2-T4 laryngeal cancer and 185 T1-T4a bladder cancer patients enrolled on the ARCON and bladder carbogen nicotinamide (BCON) phase III randomized trials of radiotherapy alone or with carbogen and nicotinamide (CON), respectively. Customized TaqMan low density arrays (TLDA) were used to assess expression of the 26-gene signature using quantitative real-time PCR. The median expression of the 26 genes was used to derive a hypoxia score (HS). Patients were categorized as TLDA-HS low (less than median) or TLDA-HS high (greater than median). The primary outcome measures were regional control (RC; ARCON) and overall survival (BCON). Laryngeal tumors categorized as TLDA-HS high showed greater benefit from ARCON than TLDA-HS low tumors; 5-year RC was 81% (radiotherapy alone) versus 100% (CON) for TLDA-HS high (p = 0.009). For TLDA-HS low, 5-year RC was 91% (radiotherapy alone) versus 90% (CON; p = 0.90); TLDA-HS did not predict benefit from CON in bladder cancer. The authors concluded that the 26-gene hypoxia signature predicted benefit from hypoxia-modifying treatment in laryngeal cancer. Moreover, they stated that these findings need to be evaluated in a prospective clinical trial.

Janssens et al (2014) noted that anemia is associated with poor tumor control. It was previously observed that ARCON can correct this adverse outcome in patients with head and neck cancer. These researchers attempted to validate this observation based on data from a randomized trial. Of 345 patients with cT2-4 laryngeal cancer, 174 were randomly assigned to AR and 171 to ARCON. Hemoglobin levels, measured before treatment, were defined as low when less than 7.5 mmol/L for women and less than 8.5 mmol/L for men. The hypoxia marker pimonidazole was used to assess the oxygenation status in tumor biopsies. Data were analyzed 2 years after inclusion of the last patient. Pre-treatment hemoglobin levels were available and below normal in 27 of 173 (16%) AR-treated patients; and 27 of 167 (16%) in ARCON-treated patients. In patients with normal pre-treatment, hemoglobin levels treatment with ARCON had no significant effect on 5-year loco-regional control (LRC, 79% versus 75%; p = 0.44) and disease-free survival (DFS, 75% versus 70%; p = 0.46) compared with AR. However, in patients with low pre-treatment, hemoglobin levels ARCON significantly improved 5-year LRC (79% versus 53%; p = 0.03) and DFS (68% versus 45%; p = 0.04). In multi-variate analysis including other prognostic factors, pre-treatment hemoglobin remained prognostic for LRC and DFS in the AR treatment arm. No correlation between pre-treatment hemoglobin levels and pimonidazole uptake was observed. The authors concluded that results from the randomized phase III trial supported previous observations that ARCON has the potential to correct the poor outcome of cancer patients with anemia.

Yip and Alonzi (2013) noted that prostate cancer hypoxia is associated with inferior prognosis and resistance to treatment. The use of androgen deprivation therapy, both prior to and during radiotherapy, may exacerbate underlying hypoxia. While larger radiation doses per fraction may achieve therapeutic gain, this is balanced by the reduced opportunity for re-oxygenation to take place during the course of treatment. Improving the underlying hypoxic tumor environment may therefore improve the treatment outcomes. The authors reviewed strategies to combat tumor hypoxia, with particular focus on the use of carbogen gas breathing concurrently with radiotherapy.

Also, the National Comprehensive Cancer Network’s clinical practice guidelines on “Head and neck cancers” (Version 2.2013), “Bladder cancer” (Version 1.2014) and “Prostate cancer” (Version 1.2014) do not mention the use of carbogen therapy as a therapeutic option.

Hsiao and Huang (2014) described the first case of partial vision recovery in a 32-year old woman with iatrogenic retinal artery occlusion (RAO) following glabella calcium hydroxyapatite (CaHA) injection, and explored appropriate diagnostic and therapeutic measures according to a literature review. The subject had left eye RAO and a bilateral visual field defect following CaHA injection into the glabella region. Topical and systemic intra-ocular pressure lowering agents, isovolemic hemodilution, globe massage, and anti-coagulation with acetylsalicylic acid were prescribed. Carbogen inhalation and oral corticosteroids were also given. In addition to the above therapies, hyperbaric oxygen therapy (HBOT) was implemented as adjuvant treatment. The final best corrected visual acuity (BCVA) of the left eye
improved from hand motion at 15 cm to 0.1. Improved retinal circulation and decreased retinal vessel leakage were found in the follow-up fluorescein angiography. However, there were still multiple emboli in the conjunctival and retinal arteries. The authors concluded that this was the first case report on partial recovery of BCVA after iatrogenic RAO following cosmetic CaHA injection. Because no reliable treatments have been reported for such complications, HBOT may be considered as an alternative adjuvant therapy. There is insufficient evidence that Carbogen inhalation is effective in treating RAO.

Cervical Cancer:

van Weelden et al (2014) noted that chemo-radiation (CRT) is the standard therapy for advanced stages of cervical cancer. In developing countries, where 80 % of cervical cancers occur, this is not always available. Carbogen breathing and oral nicotinamide (CON) therapy, aimed at overcoming tumor hypoxia, has shown to improve treatment effectiveness in some epithelial tumors. These researchers examined the effect of CON during CRT of advanced stages of cervical cancer on overall survival (OS), local and regional control, and toxicity. From December 2006 to February 2010, a total of 139 patients with stage IB2 to IVA cervical cancer were non-randomly assigned to receive radiotherapy (RT) or CRT with or without CON. Differences in OS, local and regional control after 1 year, and toxicity were assessed in 113 evaluable patients; 32 patients received RT, 16 received CRT, 45 received CON-RT, and 20 received CON-CRT. The CON-RT and RT groups contained significantly more patients with a poor performance status and IIIB and IVA tumors. Despite these differences in baseline characteristics, OS and local and regional control at 1 year were not significantly different (p = 1.10 and p = 0.19, respectively). Toxicity scores also did not differ (p = 0.60 and p = 0.73 for acute and late toxicity). The authors concluded that addition of CON to standard (chemo)radiation resulted in comparable survival and control rates. They stated that the effect of CON might be under-estimated due to differences in baseline characteristics. The authors noted that because chemotherapy cannot always be (completely) administered in low-resource settings, CON could be a worthy substitute; the CON treatment is feasible and safe. This study did not establish the effectiveness of carbogen inhalation therapy for the treatment of cervical cancer.

UpToDate reviews on “Management of early-stage cervical cancer” (Straughn and Yashar, 2016a), “Management of locally advanced cervical cancer” (Straughn and Yashar, 2016b) and “Management of recurrent or metastatic cervical cancer” (Wright, 2016) do not mention carbogen inhalation therapy as a therapeutic option.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Cervical cancer” (Version 1.2016) does not mention carbogen inhalation therapy as a therapeutic option.

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<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<td>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</td>
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<tr>
<td>Carbogen inhalation therapy:</td>
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<td>No specific code</td>
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<tr>
<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
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<tr>
<td>C00.0 - C00.9  Malignant neoplasm of lip</td>
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<td>C01 - C06.9  Malignant neoplasm of oral cavity</td>
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<tr>
<td>C07 - C08.9  Malignant neoplasm of other and unspecified major salivary glands</td>
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<tr>
<td>C11.0 - C11.9  Malignant neoplasm of nasopharynx</td>
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</table>
The above policy is based on the following references:

31. Straughn JM Jr., Yashar C. Management of locally advanced cervical cancer. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2016b.
32. Wright JD. Management of recurrent or metastatic cervical cancer. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2016.
There are no amendments for Medicaid.