ADDITIONAL MATERIALS AVAILABLE ON THE HEI WEBSITE

Research Report 192

Multicenter Ozone Study in oldEr Subjects (MOSES): Part 1. Effects of Exposure to Low Concentrations of Ozone on Respiratory and Cardiovascular Outcomes

Mark W. Frampton et al.

Additional Materials 6. List of Adverse Events by Center

These Additional Materials were not formatted or edited by HEI. These documents were part of the HEI MOSES Review Panel's review process.

Correspondence may be addressed to Dr. Mark W. Frampton, Pulmonary & Critical Care, University of Rochester Medical Center, 601 Elmwood Ave., Box 692, Rochester, NY 14642-8692; e-mail: *mark_frampton@urmc.rochester.edu*.

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Table 1. Summary of adverse events by center and status

	URMC N= 13 N	UNC N=19 N	UCSF N=7 N	Overall N=39 N
Relationship of AE to study				
Definitely Related	1	4	1	6
Probably Related	0	5	0	5
Possibly Related	0	5	2	7
Not related	12	5	4	21
Severity				
Grade 1 (Mild)	0	7	6	13
Moderate (Grade 2)	13	11	1	25
Grade 3 (Severe)	0	1	0	1
Grade 4 (Life Threatening)	0	0		0
Outcome				
Recovered/resolved	13	15	7	35
Recovering/resolving	0	3	0	3
Not Recovering/not resolving	0	0	0	0
Recovered/resolved with sequelae	0	0	0	0
Fatal	0	0	0	0
Unknown	0	1	0	1
Action Taken				
Study treatment/procedure stopped permanently	1	0	0	1
Study procedure/treatment temporarily stopped and restarted	1	1	2	4
No action taken	0	11	1	12
Other	11	7	4	22

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Table 2. List of all Adverse Events for subjects who completed all 3 exposures by center

URMC (N=13):

Subject #	AE #	Report type	Study Day*	Severity	Relationship to study	Action taken	Outcome	Narrative
11023	1	Initial	2	Moderate (Grade 2)	Definitely related	Study treatment/ procedure stopped	Recovered/resolved	Following inhalation of 3% saline, subject had decrease i FEV1 of 10-19%. After subsequent inhalation of 3% saline, per protocol, FEV1 dropped 25%, with mild tightness in chest. Sputum induction stopped, MD paged, and albuterol given, with improvement in FEV1 to above baseline. Subject had some cough, nasal stuffiness, and rhinorhea over next 2 days, similar to allergy symptoms in past.
11227	1	Initial	1	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject was given 650mg Tylenol for a headache she felt just starting. Pain was a 1 out of 10. Headache resolved when she went to sleep that night.
11249	1	Initial	1	Moderate (Grade 2)	Not related	Study procedure/treatment temporarily stopped and restarted	Recovered/resolved	Subject had trace headache at the end of the exposure (11:02am). Post-exposure spirometry increased severity of headache with pain of 3 out of 10 (11:30am). Subject completed 2 successful spirometry trials but then had several unsuccessful trials. Coordinator stopped spirometry without getting 3rd successful trial so that subject could return to the Clinical Research Center where she was given 650mg Tylenol and rest. Subject had no headache at 14:10. Headache was likely related to stopping caffeine.
11249	2	Initial	41	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Head ache was first felt by subject at noon on 16JUL2013. At 14:39 she was given 650mg Tylenol by Clinical Research Center nurse. Subject reported pain from headache was 5 out of 10 at the time she took Tylenol. At 15:15 subject reported that she no longer had a headache. Headache was likely related to stopping caffeine.
11249	3	Initial	83	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject was given 65omg Tylenol for headache pain of 3 out of 10, which started at 10:30am on 27AUG2013.

11307	1	Initial	1	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject was given 650mg Tylenol on 18Sep2013 at 8:25 for a headache (pain of 3 out of 10) that began 15:00 on 17Sept2013.
11307	2	Initial	36	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject was given 650mg Tylenol on 22OCT2013 at 11:53 for a headache (pain 1 out of 10) that began at 9:30 on 22OCT2013. Headache stopped at 20:00 on 22OCT2013.
11307	3	Initial	63	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject given 650mg Tylenol at 13:30 on 18NOV2013 for headache (pain 1 out of 10) that started 8:00 on 18NOV2013 and ended 20:00 on 18NOV 2013.
11307	4	Initial	64	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject given 650mg Tylenol at 15:25 for headache (pain 1 of 10) that started at 12:00 on 19NOV213 and ended 19:00 on 19NOV2013.
11318	1	Initial	1	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject had moderate headache from 6:00am on 6/11/13 to 6/12/13 at 3:30pm. Headache likely related to stopping caffeine. Subject was given 650mg Tylenol each day.
11318	2	Initial	41	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject arrived at the Clinical Research Center at 11:30am on 22JUL2013 complaining of a headache that had started the day before at 8:00. CRC nurse gave subject 650mg Tylenol at 12:30 for headache pain of 2 out of 10. Subject was also given 650mg Tylenol at 7:00 on 23JUL20013 and 14:09 on 23JUL2013. Tylenol did not reduce the pain from the headache and it remained at 2 our ot 10 until she reported that her headache was gone at 10:00 on 24JUL201. Headache was likely related to stopping caffeine.
11318	3	Initial	71	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Headache started at 8:20am on 20AUG2013 at the start of the first rest period during the exposure. Subject was given 650mg Tylenol at 11:50am when subject returned to the Clinical Research Center for headache with pain 2 0r 3 out of 10. At 14:06, subject reported that she had no headache.
11523	1	Initial	50	Moderate (Grade 2)	Not related	Other	Recovered/resolved	Subject was given 650mg Tylenol for a mild headache (pain 2 out of 10) at 12:50 on 18NOV2014. 30 minutes later she no longer had a headache.

*****Number of days before or after randomization

UNC (N=19):

Subject #	AE #	Report type	Study Day*	Severity	Relationship to study	Action taken	Outcome	Narrative
21036	1	Initial	1	Mild (Grade 1)	Possibly related	No action taken	Recovered/resolved	Subject reported a headache on the symptom questionnaire after exposure. It continued through the evening. She took 500mg Tylenol x 3 n the evening and 500mg Tylenol in the am. She reported via email that it resolved in the afternoon of the post exposure day.
21036	2	Initial	23	Moderate (Grade 2)	Probably related	No action taken	Recovered/resolved	subject reported vomiting with headache after NTG while at the hotel. Vomiting is not expected with headaches and has been reported to IRB.
21036	3	Initial	23	Moderate (Grade 2)	Probably related	No action taken	Recovered/resolved	Subject had headache after NTG administration. It progressed while she was at the hotel. she applied Ice and went to bed for treatment
21036	4	Initial	24	Moderate (Grade 2)	Probably related	No action taken	Recovered/resolved	Subject reported trace headache on the symptom questionnaire after NTG/BAU. It progressed when she left and she took 500mg tylenol which resolved the headache
21036	5	Initial	44	Mild (Grade 1)	Probably related	Other	Recovered/resolved	Subject reported headache which started yesterday after NTG. It remained overnight, but resolved after breakfast this am.

21070	1	Initial	0	Severe (Grade 3)	Definitely related	Other	Recovered/resolved	Moses subject 21070 was given 0.4mg. sublingual nitroglycerin during the Brachial Artery Ultrasound measurements on day 1 of the 3 day exposure session. This subject (who is ordinarily free of headaches and has never had migraines) had a slight residual bi-fronto-temporal, intermittently throbbing headache after the BAUS measurements. No photophobia. No "aura" but later felt "sick" - as if she might be developing "flu". The bilateral headache gradually increased in intensity, became associated with nausea, and led to full scale vomiting at 8PM. Fell asleep at 9PM. Headache awakened her at 3AM. Slept again from 4:00-5:30AM (awakened by clock alarm). She arrived at the research lab at 7:15am, and she still noted some headache and distaste for food. She was given 650 mg of acetaminophen at the research lab after consulting with the principal investigator by phone at 7:30AM. She gradually began to feel better, with near complete resolution of headache by about 8am. She continued to complain of mild nausea. However, after lunch this also resolved, and with no more vomiting. The chamber exposure started at 8:35AM. Her BP was stable and unchanged from her baseline, and a physical exam was unremarkable. She noted again at the end of the exposure day (approximately 4pm) that she had a very slight headache. No nitroglycerin was administered during the Brachial Artery Ultrasound on the exposure day. She was discharged from the lab with contact information for Dr. Bromberg, and with instructions to call with any concerns, but particularly any increase in the symptoms noted in this report. She did decide to use acetaminophen prior to bedtime, and she slept well. She awoke on day 3 of the exposure session with complete resolution of symptoms

21070	2	Initial	43	Moderate (Grade 2)		No action taken	Recovered/resolved	Subject woke with a mild headache. She forgot her night guard when she went to the hotel, so she slept without it. She rarely forgets to use it as she states she always wakes with a headache when she does not use it. She took Tylenol when she arrived home after the study visit which completely resolved the headache.
21070	3	Initial	44	Mild (Grade 1)	Not related	No action taken	Unknown	No narrative
21105	1	Initial	1	Mild (Grade 1)	Probably related	No action taken	Recovering/resolving	Skin lesion. 13 Feb 2013: there are two 5-mm diameter lesions with central 2mm whitish area lesions on dorsal aspect of left forearm which resulted from scratches caused by rubbing against the left handrail of the treadmill 2 weeks ago. These were initially scratches - but the volunteer rubbed cocoa-butter into them which I think resulted in irritation or infections. Currently these are both superficial, minimally if at all tender. No lymphadenitis, no epitrochlear node enlargement. No exudate from the two lesions. 04 Mar 2013: scar tissue (2mm lesions) over left forearm , healed well.
21150	1	Initial	99	Moderate (Grade 2)	Possibly related	Other	Recovered/resolved	Subject awoke in hotel with a mild headache. After leaving the research unit at the end of exposure day it was still preset so she took a single 325mg Tylenol which resolved the headache
21194	1	Initial	60	Moderate (Grade 2)	Definitely related	Other	Recovered/resolved	ECG patches were placed on this subject only for 10 minute intervals to measure HRV rather than for 24 hours. On arrival to research lab 22-nov-2013 a rash was noted in the area under the breast where the patches had been placed. Subject treated with1% hydrocortisone for 24 hours
21194	2	Initial	6	Moderate (Grade 2)	Definitely related	Other	Recovering/resolving	Subject developed itch/redness in area under the breast from Holter patches.
21194	3	Initial	46	Moderate (Grade 2)	Definitely related	Other	Recovered/resolved	Subject noted rash with small blisters in areas on her chest where the ECG holter patches were placed. She used topical 1% hydrocortisone cream for 24 hours which resolved the rash.

21207	1	Initial	132	Moderate (Grade 2)	Not related	Study procedure/ treatment temporarily stopped and restarted	Recovering/resolving	No narrative
21354	1	Initial	58	Mild (Grade 1)	Not related	No action taken	Recovered/resolved	Systolic blood pressure reading was outside normal limits. Subject was asymptomatic. Subsequent systolic reading prior to discharge was within normal limits (112mm hg at 09:17).
21536		Initial	22	Mild (Grade 1)	Possibly related	No action taken	Recovered/resolved	A single blood pressure reading showed a systolic blood pressure of 87mmHg
21638	1	Initial	1	Mild (Grade 1)	Possibly related	No action taken	Recovered/resolved	Systolic blood pressure exceeded normal values
21638	2	Initial	1	Moderate (Grade 2)	Possibly related	Other	Recovered/resolved	Subject developed headache which became worse during post exposure spirometry. she took Tylenol 325mg at 16:3- (once she arrived home) with resolution of the headache
21638	3	Initial	0	Moderate (Grade 2)	Not related	No action taken	Recovered/resolved	Subject noted back pain in the evening while at the hotel. it continued intermittently during the exposure day. It was improving after she returned to her home.

*****Number of days before or after randomization

UCSF (N=6):

Subject #	AE #	Report type	Study Day	Severity	Relationship to study	Action taken	Outcome	Narrative
31209	1	Initial	88	Mild (Grade 1)	Not related	Other	Recovered/resolved	Subject 31209 reported dull throbbing pain to left buttock, and posterior of thigh and calf. Onset 04Jan2014 @ 0600. Symptoms are most severe when sleeping or supine. On a scale of 0 (none) to 5 (severe) subject notes a 3. Does snot feel it will affect his ability to exercise. No meds taken. John Balmes consulted with subject and plans to perform an exam Wednesday, 08Jan2014 if symptoms persist. 08Jan202214: John Balmes, MD: Notes no sciatica and subject referred to General Medicine Clinic at SFGH. 13Jan2014: Naproxen Sodium 200 mg Prn before exercise and for pain. 24Mar2014: Reports resolution of left leg pain on 17Mar2014, time unknown.

31265	1	Initial	50	Mild (Grade 1)	Definitely related	Other	Recovered/resolved	At the subject's 9Jun2014 study visit, the subject reported 2 small colored areas (LRQ and LLq) on his stomach. Michael Guarnieri, MD examined the subject and notes hyperpigmentation on the subjects stomach and recommended mild OTC hydrocorticosteroid cream be applied. These spots are where 2 of 10 Ambu Blue Sensor VLC: VLC-00-S/10, lot # 1550010 pads were placed April 29-30, 2014. 12Jun2014: John Balmes, MD examined the subject and notes: Participant reports two areas of skin rash where the Holter ECG pads were placed at the last set of exposure (4/29/14)-when I examined the area there was discoloration in a round pattern consistent with lead placement-topical corticosteroid cream was applied and the participant stated that he would buy some and continue to apply it. 16Jun2014: Subject reports no new spots, no itching and that the discoloration appear to be fading albeit slowly. Subject asked to follow up with us when resolved. 25Jul2014: Subject reports that he will apply OTC hydrocorticosteroid cream for one week. 21Aug2014: No obvious benefit noted with the OTC hydrocorticosteroid cream. Notes he will probably see his primary care physician. He was offered to be seen by a UCSF Dermatologist. 25Aug2014: Offered to be seen by a UCSF Dermatologist. 3Sept2014: John Balmes, MD reports that the UCSF Dermatologist said the resolution/recovery would be very slow and suggest a follow up visit in Sept 2015. 1Jul2015: Subject reports complete resolution of spots. Although he was not sure of the date, he agreed 1Jan2015 be the resolution date.
31356	1	Initial	-17	Mild (Grade 1)	Not related	Other	Recovered/resolved	On 16 Jun 2014, subject reported the onset of a lower left back pain due to a pinched nerve. This started on 14Jun2014, and Ibuporfen 2 tabs PRN for pain was taken, This was reported20Jun2014 to resolve 19Jun2014 @ 08:30am. No additional treatment incurred.

31403	1	Initial	0	Moderate (Grade 2)	Not related	No action taken	Recovered/resolved	Subject 31403 reported moderate headache at 16:30 - 17:00 during her commute home after EXP1. It resolved on its own with no OTC medicine or other treatment intervention.
31403	2	Initial	15	Mild (Grade 1)	Possibly related	Study procedure/ treatment temporarily stopped and restarted	Recovered/resolved	30Mar2015: Subject reported having transient waves of exhaustion beginning 25 Mar 2015 @ 05:45 to 5 Apr 2015 @ 08:30. It resolved with no medical intervention or treatment.
31403	3	Initial	20	Mild (Grade 1)	Possibly related	Study procedure/ treatment temporarily stopped and restarted	Recovered/resolved	Subject reported tenderness to touch of lymph nodes at neck when applying skin cream to neck area 30 Mar 2015 @ 06:30. Resolved: no tenderness noted 01 April 2015 @ 06:00.

*****Number of days before or after randomization